

# The Lipid-Lowering Effect of Tenofovir/Emtricitabine: A Randomized, Crossover, Double-Blind, Placebo-Controlled Trial

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**Background.** It is unknown if tenofovir disoproxil fumarate (TDF), which is often coformulated with the lipid-neutral emtricitabine (FTC), has a lipid-lowering effect.

**Methods.** We performed a randomized, crossover, double-blind, placebo-controlled clinical trial on human immunodeficiency virus type 1 (HIV-1)-infected subjects with HIV-1 RNA < 50 copies/mL during ≥6 months on stable darunavir/ritonavir (800/100 mg once daily) or lopinavir/ritonavir (400/100 mg twice daily) monotherapy, fasting total cholesterol (TC) ≥200 mg/dL or low-density lipoprotein cholesterol (LDL-c) ≥130 mg/dL, and no lipid-lowering drugs. In arm 1, TDF/FTC was added for 12 weeks, followed by 12 weeks of placebo (washout) and 12 additional weeks of placebo (placebo period). Subjects in arm 2 added placebo for 12 weeks (placebo period) followed by TDF/FTC for 12 weeks and placebo for 12 additional weeks (washout). The primary endpoint was change in median fasting TC levels.

**Results.** Of 46 subjects enrolled, 56% received darunavir/ritonavir and 44% lopinavir/ritonavir. Exposure to TDF/FTC reduced TC from 234 to 205 mg/dL ( $P < .001$ ), LDL-c from 155 to 128 mg/dL ( $P < .001$ ), and high-density lipoprotein cholesterol (HDL-c) from 50.3 to 44.5 mg/dL ( $P < .001$ ). It also decreased the proportion of subjects with fasting TC ≥200 mg/dL from 86.7% to 56.8% ( $P = .001$ ), and LDL-c ≥130 mg/dL from 87.8% to 43.9% ( $P < .001$ ). After 12 weeks, TDF/FTC exposure was associated with lower TC and LDL-c levels than placebo ( $P = .001$  and  $P = .002$ , respectively). The TC/HDL-c ratio and triglyceride levels did not change with TDF/FTC exposure.

**Conclusions.** Coformulated TDF/FTC has an intrinsic lipid-lowering effect, likely attributable to TDF.

**Clinical Trials Registration.** NCT01458977.

**Keywords.** lipid-lowering effect; coformulated tenofovir/emtricitabine; total cholesterol; LDL cholesterol; boosted protease inhibitor monotherapy.

Monotherapy with boosted protease inhibitors (PIs) as a simplification strategy is recommended by some guidelines as an optional regimen for selected

subjects [1, 2]. Nevertheless, dyslipidemia has been frequently associated with the use of lopinavir/ritonavir (LPV/r) [3, 4]. In addition, in the pivotal clinical trial of darunavir/ritonavir (DRV/r) monotherapy, subjects who started tenofovir disoproxil fumarate (TDF) in the triple therapy arm experienced a trend toward a decrease in total cholesterol (TC), whereas those who stopped TDF at baseline in the monotherapy arm showed increases in TC [5]. Data from routine clinical practice including subjects on DRV/r monotherapy have also reported that this strategy could worsen low-density lipoprotein cholesterol (LDL-c), mainly in subjects discontinuing TDF,

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although it may be useful to improve LPV/r-related hypertriglyceridemia [6].

Some clinical trials have also reported a more favorable lipid profile of TDF in comparison to other nucleoside reverse transcriptase inhibitors (NRTIs), in both naive and treatment-experienced subjects [7–14]. These studies, however, have not addressed whether the observed improvements are due to withdrawal of the offending agent or related to primary lipid-lowering attribute of TDF. A better understanding of TDF lipid-lowering effect could be useful for the better management of subjects with dyslipidemia and higher cardiovascular risk. In addition, TDF is usually prescribed as a coformulation with emtricitabine (FTC), which has a well-known and almost neutral metabolic impact [15]. Therefore, we aimed to assess the lipid-lowering effect of TDF by sequentially adding and withdrawing coformulated TDF/FTC from subjects with high cholesterol levels and virologically suppressive PI monotherapy.

## METHODS

### Study Population

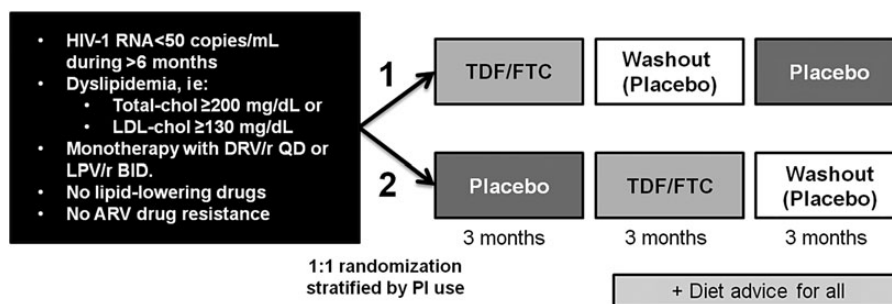
Eligible subjects included human immunodeficiency virus type 1 (HIV-1)-infected adults with hypercholesterolemia (9- to 12-hour fasting TC level  $\geq 200$  mg/dL and/or LDL-c level  $\geq 130$  mg/dL) in the last 2 consecutive tests obtained at least 4 weeks apart before screening, receiving stable PI monotherapy with DRV/r (800/100 mg once daily) or LPV/r (400/100 mg twice daily), and with HIV-1 RNA  $< 50$  copies/mL during at least 6 months before screening. The enrollment of subjects with concomitant use of lipid-lowering drugs at study entry, documented renal pathologies or creatinine clearance  $< 60$  mL/minute calculated by the Cockcroft-Gault formula, or HIV-1 resistance to any of the study agents was not allowed.

### Study Design

This was a multicenter, double-blind, randomized, placebo-controlled clinical trial using a 3-sequence, 3-period crossover design.

All subjects fulfilling inclusion criteria were randomized (1:1) to add either a coformulated once-daily fixed dose of 300/200 mg of TDF/FTC or placebo to their stable PI monotherapy. The randomization was stratified by DRV/r or LPV/r intake at baseline. TDF/FTC coformulation and placebo were provided in a double-blinded fashion over 9 months. Subjects in arm 1 initiated coformulated TDF/FTC for 12 weeks (intervention period), followed by 12 weeks with placebo (washout period), and then placebo for 12 weeks (placebo period). In arm 2, subjects initiated placebo for 12 weeks (placebo period), followed by 12 weeks with coformulated TDF/FTC (intervention period), and then placebo for 12 weeks (washout period). The washout periods made it possible to establish intrasubject comparisons. Exposures to TDF/FTC intervention and placebo periods from both arms were taken together to perform comparisons (Figure 1). All subjects received dietary counseling by a specialized dietician to promote lipid-lowering diet throughout the study. For this, the dietary intake was assessed and controlled at each visit using a 24-hour recall and a qualitative food frequency consumption questionnaire. Additionally, a review of the nutritional recommendations to promote and ensure adherence to them were performed at each visit. The dietician was also blinded for the subject's study allocation.

The primary study endpoint was change in median fasting TC levels during the 12 weeks of TDF/FTC intervention compared with placebo. Secondary endpoints were median changes in LDL-c and high-density lipoprotein cholesterol (HDL-c) levels, TC/HDL-c ratio, triglycerides, liver enzymes, serum phosphate, serum creatinine, glomerular filtration rate (GFR)



**Figure 1.** Study design: multicenter, randomized, crossover, double-blind, placebo-controlled, 3-period clinical trial. Primary endpoints: changes in median fasting total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol levels. Secondary endpoints: percentage of patients with high levels of total and LDL cholesterol (National Cholesterol Education Program Adult Treatment Panel III), and changes in triglycerides, total/HDL cholesterol ratio, CD4 cell count, liver enzymes, serum phosphate, creatinine, and glomerular filtration rate. Abbreviations: ARV, antiretroviral; BID, twice daily; chol, cholesterol; DRV/r, darunavir/ritonavir; HIV-1, human immunodeficiency virus type 1; LPV/r, lopinavir/ritonavir; PI, protease inhibitor; QD, once daily; TDF/FTC, coformulated tenofovir disoproxil fumarate/emtricitabine.

according to the Cockcroft-Gault formula, and the percentage of subjects with high TC and LDL-c levels during the 12 weeks of TDF/FTC intervention compared with placebo. Borderline high-level classification (TC  $\geq$ 200 mg/dL and/or LDL-c  $\geq$ 130 mg/dL) according to the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) guidelines [16] were considered to define high levels of TC and LDL-c. We also evaluated the percentage of subjects with virological failure (defined as 2 consecutive plasma RNA HIV-1 levels  $>$ 50 copies/mL), changes in CD4<sup>+</sup> cell count, and drug-related adverse events or toxicity during the study.

The study sample size was calculated to achieve the main study endpoint. The per protocol estimation was that a sample size of 30 individuals per group (60 subjects in total) would provide 80% power to detect a decrease in cholesterol of 38.7 mg/dL (1 mmol/L) in subjects receiving TDF/FTC if the decrease in the placebo group was 19.35 mg/dL (0.5 mmol/L), assuming a 2-sided  $\alpha$  value of .05.

The study was approved by the ethics committees of the participating centers and the appropriate health authorities, and was conducted according to the stipulations of the Declaration of Helsinki (2008). All subjects provided their written informed consent for participation. The study has been registered with ClinicalTrials.gov under the identifier NCT01458977.

### Statistical Analysis

Demographics and clinical variables were described using mean and SD, median and interquartile range (IQR), or frequency and percentage, as necessary. Longitudinal changes in cholesterol levels were analyzed using paired Student *t* test, Wilcoxon test, or Friedman *t* test when appropriate. The McNemar or Cochran test was used to compare proportions. All analyses were blinded and performed by intention to treat (ITT). Statistical analysis was performed using SPSS version 15.0 (Chicago, Illinois) and R (R Foundation for Statistical Computing, Vienna, Austria) software [17]. Differences were considered statistically significant at  $P < .05$ .

## RESULTS

Between November 2011 and May 2013, 48 subjects were randomized. One subject in each group did not initiate the study medication, and both were excluded. One subject withdrew his informed consent from the study at week 4 and another interrupted his antiretroviral treatment due to diarrhea at week 24. Therefore, the ITT analysis set included 46 subjects: 23 in each group, of which 26 (56%) were on treatment with DRV/r and 20 (44%) on LPV/r monotherapy. The median age of subjects was 43 (IQR, 40–48) years and 32 (69.6%) were male. The median time on stable PI monotherapy was 98 (IQR, 58–142) weeks. Other clinic and demographic characteristics are described in Table 1.

**Table 1. Baseline Characteristics (N = 46)**

Characteristic	No. (%)
Sex, male	32 (69.6)
Age, y, median (IQR)	43 (40–48)
Smoking <sup>a</sup>	8 (17.4)
Use of alcohol <sup>b</sup>	3 (6.5)
Time since HIV diagnosis, y, median (IQR)	10.7 (4.9–18.2)
Hepatitis C virus coinfection <sup>c</sup>	3 (6.5)
Transmission route	
Heterosexual	19 (41.3)
MSM	17 (37.0)
IVDU	3 (6.5)
Others	7 (15.2)
PI monotherapy	
Darunavir/ritonavir	26 (56.5)
Lopinavir/ritonavir	20 (43.5)
Time on stable PI monotherapy, wk, median (IQR)	98 (58–142)
CD4 <sup>+</sup> nadir, cells/ $\mu$ L, median (IQR)	213 (153–342)
CD4 <sup>+</sup> count, cells/ $\mu$ L at baseline, median (IQR)	627 (500–801)

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; IVDU, intravenous drug user; MSM, men who have sex with men; PI, protease inhibitor.

<sup>a</sup> Defined as active smoking of 1 or more manufactured or hand-rolled tobacco cigarettes, from purchased or home-grown tobacco, per day.

<sup>b</sup> Defined as alcohol consumption  $>$ 14 standard drinks per week or  $>$ 4 drinks per day for men, and  $>$ 7 standard drinks per week or  $>$ 3 drinks per day for women.

<sup>c</sup> Defined as positive results of hepatitis C virus antibody tests.

### Lipid Parameters

When intrasubject comparisons were performed, we observed decreases in median (IQR) levels of TC from 235.9 (216.5–262.9) mg/dL to 204.9 (182.9–230.5) mg/dL ( $P < .001$ ), LDL-c from 154.7 (143.7–175.4) mg/dL to 127.6 (113.3–152.7) mg/dL ( $P < .001$ ), and HDL-c from 50.3 (38.7–58.0) mg/dL to 44.5 (38.4–50.4) mg/dL ( $P < .001$ ) after 12 weeks of TDF/FTC exposure. The median (IQR) of TC/HDL-c ratio and triglyceride levels changed from 4.9 (3.9–5.9) mg/dL to 4.8 (3.8–5.6) mg/dL and from 133.7 (106.3–194.9) mg/dL to 137.3 (104.9–193.1) mg/dL ( $P = .101$  and  $P = .631$ , respectively). During the 12-week washout period, we observed increases in median levels of TC ( $P < .001$ ), LDL-c ( $P < .001$ ), and HDL-c ( $P < .001$ ), with no significant changes in TC/HDL-c ratio ( $P = .751$ ) and triglycerides ( $P = .288$ ). In addition, there were no significant changes in the median of any of lipid parameters during 12 weeks of placebo exposure (Table 2).

When periods of TDF/FTC intervention and placebo exposures were compared, there were no differences at baseline in the median levels of lipid parameters. After 12 weeks of exposure to TDF/FTC, however, we observed lower median levels of TC ( $P = .001$ ) and LDL-c ( $P = .002$ ), but similar levels of HDL-c

**Table 2. Changes in Laboratory Parameters**

Parameter	TDF/FTC Exposure			Placebo Exposure			P Value (Week 12)
	Baseline	Week 12	P Value <sup>a</sup>	Baseline	Week 12	P Value <sup>a</sup>	
TC, mg/dL	235.9 (216.5–262.9)	204.9 (182.9–230.5)	<.001	234.7 (213.5–265.9)	232.0 (204.9–255.6)	.484	.718
LDL-c, mg/dL	154.7 (143.7–175.4)	127.6 (113.3–152.7)	<.001	150.8 (127.2–177.9)	144.6 (133.0–170.1)	.772	.495
HDL-c, mg/dL	50.3 (38.7–58.0)	44.5 (38.4–50.4)	<.001	48.3 (39.7–57.0)	47.8 (38.7–58.2)	.472	.750
TC/HDL-c ratio, mg/dL	4.9 (3.9–5.9)	4.8 (3.8–5.6)	.101	4.9 (4.3–6.0)	4.9 (4.1–5.8)	.866	.858
Triglycerides, mg/dL	133.7 (106.3–194.9)	137.3 (104.9–193.1)	.631	150.1 (124.0–192.6)	141.7 (106.3–208.1)	.536	.375
Phosphate, mmol/L	1.1 (0.9–1.3)	1.1 (1.0–1.3)	.596	1.1 (1.0–1.3)	1.1 (0.9–1.3)	.817	.502
Creatinine, mg/dL	.81 (.67–0.97)	.85 (.72–0.97)	.007	.85 (.72–0.95)	.82 (.71–0.96)	.856	.664
AST, U/L	21.5 (18.0–25.0)	22.8 (18.0–31.0)	.002	21.0 (16.8–25.0)	21.0 (18.0–25.0)	.914	.973
ALT, U/L	21.0 (17.1–33.0)	24.5 (16.3–34.1)	.020	20.0 (16.4–34.0)	22.0 (15.0–33.0)	.609	.735
GGT, U/L	22.0 (17.0–34.1)	22.0 (15.0–30.0)	.862	21.5 (15.3–32.8)	21.0 (16.8–36.0)	.845	.625
AP, U/L	68.0 (58.2–84.0)	78.0 (63.6–95.8)	<.001	70.0 (60.3–89.5)	68.3 (59.0–87.0)	.261	.670
CD4 <sup>+</sup> count, cells/ $\mu$ L	610.0 (473.5–881.5)	653.5 (484.3–854.7)	.633	631.5 (513.0–937.7)	640.0 (478.0–960.0)	.861	.634

All values are expressed as median (interquartile range).

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT,  $\gamma$ -glutamyl transferase; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine coformulation.

<sup>a</sup> Intrasubject comparisons.

( $P = .159$ ), TC/HDL-c ratio ( $P = .639$ ), and triglycerides ( $P = .587$ ) in comparison to the placebo period (Table 2).

The number of subjects with high levels of fasting TC and LDL-c after 12 weeks of TDF/FTC intervention were reduced from 39 (86.7%) to 25 (56.8%), and from 36 (87.8%) to 18 (43.9%) ( $P = .001$  and  $P < .001$ , respectively). This was not observed after 12 weeks of placebo exposure, where the proportions of subjects with high levels of TC and LDL-c did not differ significantly different ( $P = .508$  and  $P = .581$ , respectively). There were 7 (15.2%) subjects with grade 3 elevations of TC or LDL-c at baseline and 2 (4.3%) subjects 12 weeks after TDF/FTC intervention ( $P = .063$ ). In comparison, there were 8 (17.4%) subjects at baseline with grade 3 elevations of TC or LDL-c whereas there were 5 (10.9%) after 12 weeks of placebo exposure ( $P = .250$ ).

### Safety

There were no virological failures in any of the treatment groups. In addition, there were no significant changes in CD4<sup>+</sup> cell counts between groups after 12 weeks of exposure ( $P = .538$ ).

After exposure to TDF/FTC, there were small but significant increases, and always below the normal upper limit, in the median of aspartate aminotransferase ( $P = .002$ ), alanine aminotransferase ( $P = .020$ ), and alkaline phosphatase ( $P < .001$ ), although there were no significant changes in  $\gamma$ -glutamyl transferase ( $P = .862$ ). In addition, the median serum creatinine level was increased ( $P = .007$ ), whereas there were no changes in serum phosphate ( $P = .596$ ) and no patient had a reduction of GFR <60 mL/hour. None of these previously mentioned parameters changed during the placebo exposure, and no differences between TDF/FTC and placebo exposures were observed (Table 2).

There were no unexpected adverse events in the study, although 1 subject on LPV/r-based treatment developed mild diarrhea, which led to study discontinuation at 24 weeks.

### DISCUSSION

This randomized double-blind, crossover, placebo-controlled study conducted in subjects with hypercholesterolemia on a stable treatment with PI monotherapy showed significant decreases in TC and LDL-c after 12 weeks of TDF/FTC coformulation addition. These effects were observed both in intrasubject comparisons and when exposures to TDF/FTC and placebo were compared. Moreover, the percentage of subjects with high levels of fasting TC and LDL-c decreased significantly. Taken together, our results suggest that TDF/FTC has an intrinsic lipid-lowering effect.

Although recruitment of study subjects was lower than planned by our per protocol sample size calculation, differences between groups in the main study endpoint were larger than initially estimated. Thereby, our study retained full power (calculated power: 100%) to detect differences in the main endpoint.

Our results are concordant with prior studies aimed to specifically evaluate the effect of TDF on lipid profile [7, 18], although some important differences in the study designs should be highlighted. In the AIDS Clinical Trials Group A5206 study, another double-blind, randomized, placebo-controlled, crossover study, TDF significantly decreased total, non-HDL, and LDL cholesterol in dyslipemic subjects with virological suppression [18]. However, the number of subjects included was small and they were on heterogeneous antiretroviral treatments, including PI and zidovudine in most cases at the time of TDF addition. Another study, was a multicenter randomized trial also performed on subjects treated with a heterogeneous antiretroviral treatment [7]. Its design was not blinded and not crossover, and stable lipid-lowering treatment was allowed. Therefore, similar to other studies where lipid parameters improved after the switch to TDF [8–12, 19], it is difficult to determine with these studies whether the observed improvements were due to withdrawal of the offending agent or related to the primary lipid-lowering attribute of TDF. In our study, the effect on lipid parameters of baseline treatment was better controlled, as it included only subjects with 2 kinds of boosted PI in monotherapy and the confounder effect of the prior NRTI backbone was not present. In addition, other external factors of confusion such as concomitant use of other lipid-lowering drugs and diet were not permitted in the former, and well controlled in the latter. It is noteworthy that a significant decrease in HDL-c after TDF/FTC exposure was also observed, and then TC/HDL-c ratio remained stable. Although this is concordant with findings of other studies [7, 19], its impact on cardiovascular risk and the possible mechanisms for HDL-c decreasing as well as the lipid-lowering effect of TDF remain unclear. In addition, significant changes in other safety parameters were observed. Small increases in serum creatinine, aminotransferases, and alkaline phosphatase were observed after exposure to TDF/FTC. However, changes in these parameters were not different from placebo after 12 weeks of exposure and fluctuated within normal limits. Although other safety parameters such as proteinuria or bone markers were not evaluated, increases in serum creatinine, aminotransferases, and alkaline phosphatase are consistent with the TDF/FTC safety profile [20–22]. All of these changes are probably not clinically relevant in the short term. Of note, this study was not designed to evaluate the long-term toxicity of TDF/FTC, so our results do not provide additional knowledge to the well-established long-term safety profile of this coformulation.

There are several limitations to this study. We used FTC coformulated with TDF. FTC, however, has a well-known and almost neutral metabolic impact [15]. Thus, FTC is probably not a confounding factor regarding the main study lipid-effect endpoints. Additionally, and despite the potentially beneficial effect of TDF/FTC coformulation, only changes in serum lipids were

evaluated and not in lipoprotein subclasses, or number and size of LDL particles, making it difficult to extrapolate the impact on long-term cardiovascular risk. Moreover, the clinical implications on cardiovascular risk of a reduction in HDL-c and the inability of TDF/FTC coformulation to improve the TC/HDL-c ratio are also unclear. Nevertheless, there are no specific pharmacologic interventions to raise HDL-c, and current lipid-lowering measures, including pharmacologic treatments, are targeted to improve LDL-c [1, 16].

Nevertheless, the main strength of our study is that it demonstrates an intrinsic lipid-lowering effect of TDF/FTC, which is likely attributable to TDF. In fact, this effect may be another factor to consider in the management of dyslipidemia, together with other standard approaches, such as diet or addition of lipid-lowering drugs. In addition, this study provides insights into TDF-sparing regimens, suggesting indirectly that these regimens should be used carefully in subjects with dyslipidemia.

Dyslipidemia is a common adverse event of antiretroviral therapy [23, 24], and it is frequently observed with boosted PI-based treatments [24, 25]. In addition, TDF effects may be influenced by a higher-than-expected plasma concentration due to the known drug–drug interaction with boosted PI and TDF [26, 27]. In this context, the use of TDF as an NRTI backbone seems to provide subjects with virological suppression and a favorable lipid profile. Nevertheless, subjects with dyslipidemia usually share other comorbidities and risk factors that might favor the potential risk of development of bone and kidney toxicity associated with TDF [20–22]. For this reason, the use of lipid TDF/FTC properties should be considered on an individual basis, and clinical trials aimed at evaluating the mechanism by which tenofovir acts as a lipid-lowering agent are desirable.

In conclusion, this study demonstrates the intrinsic cholesterol-lowering effect of TDF/FTC coformulation, which is likely attributable to TDF. The long-term clinical impact of such effect should be further explored. For the moment, our data suggest caution when using TDF-sparing strategies in subjects with dyslipidemia and/or elevated cardiovascular risk.

## Notes

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**Author contributions.** J. R. S., J. M. L., E. N., R. P., and B. C. conceived and contributed to the study design; J. R. S., M. S., A. C., J. M. L., J. N., C. E., D. P., E. R., R. P., and E. N. contributed to the inclusion of subjects and drafting of the manuscript; I. B. contributed to data collection; C. E. contributed as a dietician; J. R. S., M. S., A. C., J. M. L., J. N., D. P., E. R., R. P., E. N., and B. C. provided critical revisions of the manuscript for important intellectual content. The authors had full access to the data, and the corresponding author had the final responsibility for submitting the manuscript for publication.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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