HSOA Journal of Antivirals, Antiretrovirals Research & Therapy

Research Article

# Variations in Lipid Levels and Cardiovascular Risk in Patients Switched from Tenofovir to Darunavir in Monotherapy

**Carlos Tornero*, Mariangeles Martinez, Marina Llopis, Simona Cioaia and Inmaculada Poquet**

*Department of Internal Medicine, Hospital Francesc Borja Gandia, Valencia, Spain*

## Abstract

The lipid-lowering effect of tenofovir may be lost when the drug is suspended to simplify the treatment of HIV infection to monotherapy, and this in turn can increase cardiovascular risk. An analysis is made of the evolution of the lipid levels of 38 patients switched from tenofovir/emtricitabine to monotherapy with darunavir/ritonavir. Patients taking lipid-lowering medications were excluded. Over the subsequent 6 months the patients showed increases in total cholesterol, LDL-cholesterol and HDL-cholesterol, though no increase in calculated cardiovascular risk was observed. The suspension of tenofovir therefore resulted in a compensatory effect upon lipid levels but had no effect upon cardiovascular risk.

## Variations in Lipid Levels and Cardiovascular Risk in Patients Switched from Tenofovir to Darunavir in Monotherapy

In some patients, simplification to Monotherapy (M) with Protease Inhibitors (PIs), suspending the nucleoside analog reverse transcriptase inhibitors after a period of effective treatment, may be an effective strategy for reducing the number of tablets, toxicity and costs. The scheme most widely used and with the greatest accumulated experience to date is probably suspension of the combination Tenofovir Disoproxil, Fumarate/emtricitabine (TDF/FTC), leaving Darunavir with Ritonavir (D/R) [1,2]. Some studies have observed lipid alterations with M that could be attributed to loss of the lipid-lowering effect of tenofovir [3], and which might modify the estimated Cardiovascular Risk (CVR). This in turn could increase the need for statin therapy, which would largely offset the appeal of M. Considering the importance of adequate management of CVR in HIV-infected patients, the present study evaluates the changes in lipid parameters and calculated CVR in the patients in our center who received treatment simplification to M with D/R, following the suspension of TDF/FTC.

***Corresponding author:** Carlos Tornero, Department of Internal Medicine, Hospital Francesc Borja Gandia, Valencia, Spain, Tel: +34 616542499; E-mail: tornero_car@gva.es; ctornero@ono.com

**Citation:** Tornero C, Martinez M, Llopis M, Cioaia S, Poquet I (2015) Variations in Lipid Levels and Cardiovascular Risk in Patients Switched from Tenofovir to Darunavir in Monotherapy. J Antivir Antiretrovir Res Ther 1: 001.

**Received:** November 22, 2015; **Accepted:** December 31, 2015; **Published:** January 20, 2016

## Material and Methods

A retrospective observational study was made of all patients receiving treatment with D/R + TDF/FTC in which therapy was simplified to M for different reasons. The included patients were not using lipid-lowering drugs, presented the information needed to calculate CVR, and had data referred to basal total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels, as well as an undetectable viral load and lipid profile determined less than 6 months before the change in treatment. The measurements were made under fasting conditions using the routine techniques and calculating LDL-cholesterol based on the Friedewald formula when the triglyceride levels were under 400 mg/dl. Candidates for M were required to have undetectable viral loads for at least one year, with treatment adherence of over 95% as determined from the returned medication counts. Cardiovascular risk was calculated at baseline and after M using the Framingham formula and the weighted equation of the ACC/AHA 2013 guides [4]. The variations were analyzed using the SPSS version 13 statistical package, applying the Student t-test for paired data, and accepting statistical significance for $p < 0.01$.

## Results

Of the approximately 400 patients followed-up on annually in our center, 57 had received M at some time, and of these subjects, 39 met the study inclusion criteria: 65% were males, and the mean age (± standard deviation) was 47.3 ± 11.1 years. Two patients were excluded due to a lack of control laboratory tests, 5 because of treatment with lipid-lowering drugs, and the rest due to M in the form of lopinavir and/or a switch from treatment regimens without tenofovir.

As regards the CVR factors, 51.3% were smokers, 20.5% had arterial hypertension, and 7.7% were diabetics. The total cholesterol, LDL-cholesterol and HDL-cholesterol levels increased significantly after M, but the estimated 10-year CVR showed practically no changes when calculated with both the Framingham formula and the weighted equation of the ACC/AHA, since the rise in total cholesterol was compensated by the increase in HDL-cholesterol (Table 1 and 2). Consequently, there were also no variations in the indications of statin therapy according to the recommendations of the ACC/AHA following M.

| | B (n=39) | P-M (n=39) |
|---|---|---|
| Total -C | 173.4 (32.7) | 194.1 (37.1) (*) |
| LDL-C | 97.1 (26.3) | 111.2 (25.1) (*) |
| HDL-C | 45.8 (16.1) | 52.0 (19.0) (*) |

**Table 1:** Cholesterol levels variations, (mg/dl).

Mean - Standard deviation; B - Basal; P-M - Post-monotherapy

## Discussion

Relatively recent studies described reductions in non-HDL-cholesterol on adding TDF to stable treatment in small patient groups, and

| | CVR: B | CVR: P-M |
|---|---|---|
| CVR-F | 8 | 7.5 |
| CVR-WE | 5.7 | 5.6 |

**Table 2:** 10 years cardiovascular risk.

B - Basal; (CVR) - CVR-F Framingham formula; CVR-WE - Cardiovascular Risk-Weighted Equation of the ACC/AHA; P-M - Post-monotherapy

on switching from other reverse transcriptase inhibitors to TDF [5-7]. This lipid-lowering effect of TDF was also observed in HIV-negative individuals [8], though the underlying mechanism and clinical relevance are still not clear.

Strategies designed to simplify treatment by introducing M have also revealed increases in the different lipid fractions [2,3]. However, the studies in this case are heterogeneous, with conversion to M from different treatment schemes. In some cases simplification is to dual-drug therapy, the effect of lipid-lowering medications is not discarded, or the impact upon CVR is not assessed in combination with the rest of vascular risk factors.

Lastly, in a recent randomized, placebo-controlled trial involving cross-over after a washout period where dyslipidemic patients administered M with D/R or lopinavir (43%) were assigned to reintroduction of TDF/FTC or placebo, exposure to TDF was found to lower total cholesterol, LDL-cholesterol and HDL-cholesterol [9].

These reported lipid-lowering effects of TDF could be taken as an argument in favor of the use of the drug to control CVR in HIV-infected patients and against the use of M, dual-therapy or other treatment schemes without TDF. However, the trials involved are heterogeneous, and clinical studies warranting its usefulness are needed. Furthermore, the likewise reported reduction of HDL-cholesterol could have a neutral or even negative effect upon CVR, for which few treatment options are currently available.

The relevance of our study is that it involves a group of homogeneous and stable patients without lipid-lowering medications and with the same M simplification scheme. Although no clinical results are available, we can at least theoretically postulate the repercussions of TDF suspension upon CVR based on two of the equations most widely used to calculate such risk. In both cases the end effect was seen to be neutral, since the increases in total cholesterol and LDL-cholesterol were compensated by the beneficial effects of HDL-cholesterol elevation.

As limitations, our study involves a retrospective design with no control group, excludes patients receiving lipid-lowering drug treatment, and cannot rule out possible interferences due to changes in life style (diet and physical exercise) between the two measurements time points. Nevertheless, the findings do not suggest a negative effect of M with D/R upon CVR, and this may also be assumed in relation to other treatment schemes involving the suppression of TDF.

In sum, tenofovir appears to lower total cholesterol and the different cholesterol fractions, and this effect seems to be lost when the drug is suspended on switching to monotherapy. The clinical relevance of these changes is not known. However, based on the equations most widely used to calculate CVR, the effect of suspending TDF might be neutral, since the increase in total cholesterol and LDL-cholesterol could be compensated by the beneficial increase in HDL-cholesterol. The observed lipid changes therefore should not be taken as an argument against the use of M with D/R.

## References

1. Paton IN, Stöhr W, Arenas-Pinto A, Martin Fisher, Ian Williams, et al. (2015) Protease inhibitor monotherapy for long-term management of HIV infection: a randomised, controlled, open-label, non-inferiority trial. The Lancet HIV 2: 417-426.

2. Arribas JR, Horban A, Gerstoft J, Fätkenheuer G, Nelson M, et al. (2010) The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. AIDS 24: 223-230.

3. Santos JR, Moltó J, Llibre JM, Negredo E, Bravo I, et al. (2012) Antiretroviral simplification with darunavir/ritonavir monotherapy in routine clinical practice: safety, effectiveness, and impact on lipid profile. PLoS One 7: 37442.

4. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, et al. (2014) 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 129: 1-45.

5. Tungsiripat M, Kitch D, Glesby MJ, Gupta SK, Mellors JW, et al. (2010) A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206. AIDS 24: 1781-1784.

6. Valantin MA, Bittar R, De Turchis P, Bollens D, Slama L, et al. (2010) Switching the nucleoside reverse transcriptase inhibitor backbone to tenofovir disoproxil fumarateâ€Š+â€Šemtricitabine promptly improves triglycerides and low-density lipoprotein cholesterol in dyslipidaemic patients. J Antimicrob Chemothe 65: 556-561.

7. Llibre JM, Domingo P, Palacios R, Santos J, Pérez-Elías MJ, et al. (2006) Sustained improvement of dyslipidaemia in HAART-treated patients replacing stavudine with tenofovir. AIDS 20: 1407-1414.

8. Randell PA, Jackson AG, Zhong L, Yale K, Moyle GJ (2010) The effect of tenofovir disoproxil fumarate on whole-body insulin sensitivity, lipids and adipokines in healthy volunteers. Antivir ther 15: 227-233.

9. Santos JR, Saumoy M, Curran A, Bravo I, Llibre JM, et al. (2015) The lipid-lowering effect of tenofovir/emtricitabine: a randomized, crossover, double-blind, placebo-controlled trial. Clin Infect Dis 61: 403-408.