Efficacy of dual therapy with lamivudine plus darunavir boosted with ritonavir once daily in HIV-infected patients with nucleoside analogue toxicity

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Sir,

Despite the use of potent and less-toxic drugs, NRTI exposure is associated with increasing reports of toxicity.1,2 In the search of alternatives, boosted PI monotherapy is not as effective as triple therapy, with a lower rate of viral suppression and increased intermittent viraemia (blips).3 However, dual therapy with lamivudine plus a PI boosted with ritonavir has shown promising preliminary data4,5 and recently, lamivudine plus lopinavir/ritonavir twice daily has been shown to be non-inferior to triple therapy in naive patients.6

This fact prompted us to prospectively assess from January 2011 to July 2013 the efficacy of a dual regimen with the combination of lamivudine plus darunavir/ritonavir (300 mg plus 800/100 mg, once daily), used after toxicity was experienced with NRTIs. No cases of pregnancy or chronic hepatitis B virus infection were included. No patient had evidence of resistance to darunavir or lamivudine or a previous history of virological failure. The study was approved by our institutional review board (EC 182/11) and patients gave written informed consent to clinical and analytical follow-up.

Routine physical examination and laboratory tests, including CD4+ cell counts and HIV-1 RNA levels (Versant HIV-1 RNA 1.0 Assay, kPCR, Siemens Diagnostics; limit of detection, 37 copies/mL), were performed at baseline and at every 3–4 months. The glomerular filtration rate (eGFR) was estimated at every analytical determination by the Chronic Kidney Disease Epidemiology Collaboration equation and urine analysis including measurements for protein, creatinine and glucose was performed at every visit. The primary study endpoint was the proportion of patients who were free of treatment failure during 48 weeks, defined as virological failure (HIV RNA level >37 copies/mL in two successive determinations), discontinuation of any drug or reintroduction of a three-drug regimen. Transient viral replication (blip) was defined as having an HIV RNA level >37 copies/mL not confirmed in a successive determination. At each timepoint, differences with respect to baseline were compared by the Wilcoxon rank test for paired samples. A two-tailed P value of <0.05 was considered statistically significant.

Overall, 48 patients were included and had >48 weeks of follow-up. The mean age of the patients was 50 years and 65% were male. Of note, patients had an undetectable HIV RNA level for a median time of 42 months (IQR 11.3–62.8) and showed a median nadir CD4+ count of 220 cells/mm3 (IQR 101–312) and a median CD4+ count of 563 cells/mm3 (IQR 399–795) at inclusion. Also, the majority of patients (30 cases, 63%) discontinued tenofovir from the NRTI backbone (8 interrupted didanosine, 7 abacavir and 3 other), mainly due to renal issues (25, 83%). Strikingly, only 10 patients were receiving darunavir as the third drug: 13 were receiving NRTIs (3 etravirine, 3 nevirapine and 7 efavirenz) and 25 received another PI (9 atazanavir, 11 fosamprenavir and 5 lopinavir). Causes of switch varied widely according to the previous regimen.

All of the patients but one reached the study endpoint and had an undetectable HIV RNA level at 48 ± 4 weeks. Thus, the efficacy...
at 1 year was 98%. Only one patient left therapy at day 27 (2%), because of loss to follow-up. The mean CD4+ count increased by 44 cells/mm³ (IQR 18–126). There were no clinical adverse events or grade 3–4 laboratory toxicities. Transaminases did not show any significant modification after treatment simplification, in spite of 30 patients (63%) with hepatitis C virus coinfection. At week 24, a significant increase in total cholesterol (TC; from 185 to 269 mg/dL; *P* = 0.03) and the TC/HDL cholesterol ratio (from 4.09 to 4.66; *P* = 0.03; Figure 1a) was observed in patients who had interrupted tenofovir. However, these alterations were mostly transient and improved without treatment modifications at week 48. Renal function significantly improved at week 48. Thus, the overall eGFR increase (+10.1 mL/min; *P* = 0.13) was especially marked in patients interrupting tenofovir (from 77.4 to 93.6; +16.2 mL/min; *P* = 0.03; Figure 1b). Urine determinations showed improvement in

**Figure 1.** Evolution of (a) total cholesterol/HDL cholesterol ratio (boxes indicate baseline, 24 and 48 weeks successively) and (b) renal function (boxes indicate median eGFR at baseline, 12, 24 and 48 weeks successively) after switching to the combination of lamivudine plus darunavir/ritonavir once daily, according to the previous use of tenofovir. Triangles above the box and whisker plots indicate outliers.
the protein/creatinine ratio (from 171 to 126 mg/g at 12 weeks; \( P = 0.04 \)). As expected, fewer drugs and the availability of a generic formulation of lamivudine produced a mean decrease in cost of 43% (34%–52%).

In this study in the clinical setting, we show the safety and efficacy of a once-daily dual regimen with lamivudine plus darunavir/ritonavir in virologically suppressed patients with NRTI toxicity. Overall, only one patient left therapy, there were no adverse events and no cases of virological failure or transient virological blips occurred.

As the only unexpected event of this dual therapy, TC, triglycerides and the TC/HDL ratio were increased during the first 6 months when compared with baseline in patients discontinuing tenofovir, confirming the lipid-lowering effect of this drug. A similar effect was observed after interrupting tenofovir in the ATLAS study.\(^5\) However, this effect was transient and therefore its repercussions should be of limited clinical importance and related to the previous third drug.

Most of our patients changed because of renal toxicity on tenofovir and after interruption the renal function progressively improved, as shown by eGFR and urine parameters. A recent study has shown that patients with renal toxicity could have delayed improvement in renal function after tenofovir withdrawal,\(^1,7,8\) but probably it is related to the moment of change. Although this result suggests the usefulness of this dual therapy in cases of renal toxicity, a comparative evaluation is necessary.

The main limitation of our study is the lack of a control group, comparing our results with those of patients receiving triple, dual or monotherapy. In a retrospective evaluation of 435 patients receiving darunavir/ritonavir monotherapy in the clinical setting, Curran et al.\(^9\) described virological suppression at 48 weeks in 87% and discontinuation in 17%. Furthermore, 23% had blips. In the ATLAS study,\(^5\) the use of atazanavir/ritonavir plus lamivudine was associated with 90% efficacy, but a higher number of blips and adverse events were observed. Indeed, other small trials of dual therapy have shown limited efficacy, with 7 of the 44 (16%) enrolled patients discontinuing a maraviroc/raltegravir combination.\(^10\) In two recent randomized simplification studies, non-inferiority has been shown after 48 weeks of the use of lamivudine plus lopinavir or atazanavir in comparison with triple therapy.\(^\text{11,12}\)

In conclusion, 98% of our patients receiving lamivudine plus darunavir/ritonavir in the clinical setting remained free from virological failure and blips and displayed adequate tolerance, after 48 weeks, in spite of a relatively low CD4+ count nadir. Renal toxicity could improve significantly after tenofovir interruption. Thus, the results from our cohort may be very useful as they describe the effectiveness of a new strategy in routine practice.

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None to declare.