RESEARCH ARTICLE

Exploratory Analysis for the Evaluation of Estimated Glomerular Filtration Rate, Cholesterol and Triglycerides after Switching from Tenofovir/Emtricitabine plus Atazanavir/Ritonavir (ATV/r) to Abacavir/Lamivudine plus ATV/r in Patients with Preserved Renal Function

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Abstract:

Background and Objectives:
Renal toxicity due to tenofovir (TDF) has been largely described in patients with HIV infection. However, other antiretroviral drugs (such as atazanavir [ATV], especially when boosted by ritonavir, ATV/r) could perpetuate some degrees of renal impairment with or without TDF co-administration. Also, possible benefits of stopping TDF in patients without renal diseases is not well known. This study aimed at exploring evolution of renal function and lipid profile after switching from tenofovir/emtricitabine (TDF/FTC) to abacavir/lamivudine (ABC/3TC), maintaining the ATV/r component of the regimen.

Methods:
Patients in the Italian MASTER Cohort, who switched from TDF/FTC plus ATV/r to ABC/3TC plus ATV/r were included, provided that major renal diseases were not diagnosed before switching (i.e., baseline). Serum creatinine, estimated glomerular filtration rate (eGFR), total cholesterol, HDL and triglycerides were evaluated at baseline and at month 18 after switching.

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Results:
126 patients were selected (80% males). Patients were mostly Italians (92%). 79% had undetectable HIV-RNA and 44% were co-infected by HBV and/or HCV. Median age at switch was 47 years (IQR 43-55). A small but significant decrease in serum creatinine [from 1.06 mg/dl (SD: 0.3) to 0.94 mg/dl (SD: 0.2); p<0.001] with an improvement in eGFR [from 86.8 ml/min (SD: 33) to 96.4 ml/min (SD: 37); p<0.001] were observed in per protocol analysis at month 18. Also ITT analysis showed a decrease in mean serum creatinine [from 1.08 mg/dl (SD: 0.35) to 0.95 mg/dl (SD: 0.24); p<0.001] with an improvement in mean eGFR [from 86.9 ml/min/1.73m2 (SD: 24.11) to 95.8 ml/min/1.73m2 (SD: 19.99); p<0.001]. Total cholesterol increased [from 188 mg/dl (SD: 42) to 206 mg/dl (SD: 44); p<0.001] but also HDL increased as well [from 46 mg/dl (SD: 14) to 54 mg/dl (SD: 19); p=0.015]. An increase in triglycerides concentration was observed [from 162 mg/dl (SD: 144) to 214 mg/dl (SD: 109); p=0.027] in per protocol analysis. Also ITT analysis showed increases of both total cholesterol [from 187 mg/dl (SD: 43.69) to 203 mg/dl (SD: 44.10); p<0.001] and HDL fraction [from 46 mg/dl (SD: 15.49) to 52 mg/dl (SD: 17.13); p=0.002] at month 18.

Conclusion:
This analysis reports an improvement in eGFR and an increase in total cholesterol and HDL fraction at month 18 after switching to ABC/3TC plus ATV/r. Given the fact that renal function was not significantly affected at baseline, our findings may suggest the utility of a proactive switch from TDF to ABC, when otherwise indicated, in patients who cannot avoid using a nucleoside backbone.

Keywords: Highly Active Antiretroviral Therapy, eGFR, Cholesterol, Nephrotoxicity, Tenofovir, Atazanavir.

INTRODUCTION
Renal toxicity due to tenofovir (TDF) as part of highly active antiretroviral therapy (HAART) has been largely described in patients with HIV infection. Also, other antiretroviral drugs could aggravate renal damage at some degree during TDF administration [1, 2]. In particular, atazanavir boosted by ritonavir (ATV/r) may increase TDF concentrations when these two drugs are co-administered and this could aggravate renal damage [3, 4]. Moreover, some degrees of acute and chronic interstitial nephritis with crystal deposition were described in patients receiving ATV plus TDF [5, 6] and ATV could induce acute tubular injury and nephrolithiasis even without TDF administration [7]. So, it has to be seen whether renal damage occurring during TDF is reversible after TDF withdrawal, in particular when ATV/r is prescribed. In addition, the possibility to counteract or prevent worsening of renal function in patients with preserved creatinine clearance at baseline with a proactive switch from TDF to abacavir (ABC) needs to be investigated.

Dyslipidemia is common in HIV infection and antiretroviral drugs are associated to lipid abnormalities with different risks associated with different drugs. Interestingly, low levels of total cholesterol were noticed during TDF intake [8 - 10]. Therefore, the potential renal benefits from switching off TDF need to be balanced with potential damage on lipid values [11].

In fact, the ATLAS study [12] showed an improvement in renal function and an increase in total cholesterol and HDL cholesterol concentrations in patients switched from two nucleo(t)side reverse transcriptase inhibitors (one of which was TDF) plus ATV/r to lamivudine (3TC) plus ATV/r. However, this strategy should not be pursued when there is a risk of failure due to previous virological rebound or archived drug resistance associated mutations in the HIV genome. Since the ATLAS did not provide a control arm, we wanted to test the pattern of renal function and lipid profile with maintenance of two nucleoside analogue drugs (one of which was ABC).

Therefore, the present study aimed at exploring both renal function and lipid profile in patients switched from TDF/emtricitabine (TDF/FTC) to a regimen containing ATV/r and ABC/3TC.

MATERIALS AND METHODS
Italian MASTER Cohort is a large prospective observational cohort of patients living with HIV involving major Italian centres of HIV care [13]. Data from all patients included in the cohort were listed and periodically updated into a common database (Health & Notes 3.5®, Healthcare S.p.A., Naples, Italy).

An exploratory analysis in patients with normal or mild impairment of renal function (grade 1 or 2 according with Kidney Disease: Improving Global Outcomes (KDIGO) classification [14]) at baseline was conducted. All adults patients with at least 6 months of active follow-up in the Italian MASTER Cohort switched from TDF/FTC plus ATV/r to ABC/3TC plus ATV/r from 2006 to 2012 were selected. Subjects with a previous diagnosis of kidney disease were excluded from the analysis.
The statistical power for this exploratory analysis was not computed "a priori", because, at the time of designing the study, we did not find any data in this specific condition (i.e., eGFR increase in patients with normal renal function after stopping TDF) to estimate the effect size. Moreover since patients already had normal renal function, the clinical significance of a pre-defined increase in eGFR could not be hypothesized.

Baseline was defined as the time window around the switch (between 30 days before and 30 days after switching). The study end-points were assessed at baseline and at month 6, 12 and 18 after switch. The following parameters were measured: HIV RNA, CD4+ T cell count, total cholesterol, HDL cholesterol, triglycerides, serum creatinine. eGFR was estimated by CKD-EPI 2009 (Chronic Kidney Disease-Epidemiology Collaboration) formula. The equation used for calculation was: 

\[ \text{eGFR} = 141 \times \min \left( \frac{\text{serum creatinine}}{\kappa}, 1 \right) \times \left( \frac{\text{serum creatinine}}{\kappa} \right)^{1.209} \times 0.993^{\text{age}} \times 1.018 \times \left[ \begin{array}{c} \text{if female} \times 1.159 \times \text{if black} \\ \text{if male} \end{array} \right] \]

\[ \kappa = 0.7 \text{ for females and 0.9 for males, } \alpha = -0.329 \text{ for females and } -0.411 \text{ for males, min indicates the minimum of serum creatinine/} \kappa \text{ or 1, and max indicates the maximum of serum creatinine/} \kappa \text{ or 1} \] [15].

Laboratory values were analyzed both as continuous and categorical measures. Serum creatinine levels were ranked by the US Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events [16]. According to this classification, serum creatinine was ranked into five classes (no impairment, mild impairment, moderate, severe and life threatening values). eGFR values were classified according with KDIGO classification. Transitions to a lower or a higher class within patients (from baseline to month 18) were also computed [14].

**Statistical Methods**

Patient characteristics at baseline were described using descriptive statistics as appropriate. For the study outcomes measured as continuous variables, we used linear effect random regression models for repeated measures. To adjust the mean differences between baseline and month 18 after TDF switch, a multivariable model was run, including the following as covariates: age, risk factors for HIV acquisition, and CD4+ T cell count. Indeed both renal and lipid endpoints are influenced by the aforementioned factors [17, 18].

Intention to treat (ITT) and per protocol analyses were conducted. ITT analysis included all patients selected for the study, despite subsequent changes in the ABC/3TC plus ATV/r regimen. Per protocol analysis included only patients who maintained ABC/3TC plus ATV/r up to month 18. Both analyses were performed to explore possible differences in the study outcomes between ABC/3TC plus ATV/r maintained up to the end of the follow-up and further modifications occurred in the regimens. In fact, in case of consistent results of the two analyses, an effect of the switch “per se” would have been supported, as well as a possible impact of ATV/r would have been excluded.

All tests were two-sided. \( P<0.05 \) was used to define statistically significant results. All the analyses were computed using the STATA 12.0 statistical package (Stata Corporation, College Station, TX).

**Ethics Procedures**

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. All patients provided written informed consent to include their clinical and biological data in the MASTER database for scientific purposes. Data submitted by the participating clinics to the data center were anonymized. The study was approved by the Ethical Committees of the Spedali Civili Hospital of Brescia (Coordinating Centre) and of the following Institutions: University Hospital of Ferrara; "Papa Giovanni XXIII" Hospital, Bergamo; University of Bari; “San Gerardo” Hospital, Monza; Hospital of Cremona; “S. M. Annunziata” Hospital, Firenze; University of Sacred Heart, Rome.

**RESULTS**

Baseline characteristics of patients are summarized in Table 1. One hundred twenty-six patients were selected. Patients were mostly males (80%). Median age was 47 years (interquartile range, IQR 43-55) and median CD4+T count was 426/mm³ (IQR 260-620). Major risk factors for HIV acquisition were intravenous drug use (30%) and sexual transmission (heterosexual 35%; homosexual 17%). TDF/FTC plus ATV/r was first line regimen in 16% patients and second line regimen in 84% patients. HIV RNA was detectable (>50 HIV RNA copies/ml) in 21% patients at baseline. HCV-Ab positive patients were 54 (43%) and two patients (1.6%) were chronic HBsAg carriers. TDF/FTC plus ATV/r was the first line antiretroviral regimen in 20 patients (16%) and prescribed as second line regimen in 106 patients (84%).
Table 1. Baseline characteristics of patients.

| Table 1. Baseline characteristics of patients. Patients characteristics at switch from TDF/FTC plus ATV/t to ABC/3TC plus ATV/r (n=126) |
|---------------------------------------------------------------|
| **Quantitative Variables**                       | **Qualitative Variables, n (%)** |
| • Median age, years (IQR)                                                              | Gender |
| • Median CD4+T cell count (IQR)                                                         | • Males | 101 (80) |
|                                                                                       | • Females | 25 (20) |
| **Risk factors for HIV infection**                                                       |
| • IVDU                                                                                   | • IVDU | 38 (30) |
| • Homosexual/bisexual                                                                   | • Homosexual/bisexual | 22 (17) |
| • Heterosexual                                                                           | • Heterosexual | 44 (35) |
| • Heterosexual+IVDU                                                                     | • Heterosexual+IVDU | 11 (9) |
| • Other                                                                                 | • Other | 11 (9) |
| **Co-infections**                                                                        |
| • HBV and/or HCV co-infected                                                             | • HBV and/or HCV co-infected | 56 (44) |
| • Not co-infected/unknown                                                                | • Not co-infected/unknown | 70 (56) |
| **HIV RNA*                                                                              |
| • Detectable                                                                             | • Detectable | 26 (21) |
| • Undetectable                                                                           | • Undetectable | 100 (79) |
| **Line of previous regimen**                                                            |
| • First line                                                                             | • First line | 20 (16) |
| • ≥ Second line                                                                          | • ≥ Second line | 106 (84) |

 n: number, IQR: interquartile range, IVDU: intravenous drug user

A small but significant decrease in mean serum creatinine [from 1.06 mg/dl (SD: 0.3) to 0.94 mg/dl (SD: 0.2); p<0.001] with an improvement in mean eGFR [from 86.8 ml/min/1.73m² (SD: 33) to 96.4 ml/min/1.73m² (SD: 37); p<0.001] were observed from baseline to month 18 (see per protocol analysis in Table 2). Also ITT analysis showed a decrease in mean serum creatinine [from 1.08 mg/dl (SD: 0.35) to 0.95 mg/dl (SD: 0.24); p=0.001] with an improvement in mean eGFR [from 86.9 ml/min/1.73m² (SD: 24.11) to 95.8 ml/min/1.73m² (SD: 19.99); p=0.001] (Table 2). Since HIV RNA could influence renal function [19], we also analyzed separately the eight patients with HIV RNA >50 copies/ml at baseline who had undetectable HIV RNA at month 18. Seven of eight patients showed a decrease in serum creatinine and an improvement in eGFR after switching. An increase in serum creatinine with decreased eGFR was observed in only one case (serum creatinine from 1.3 to 1.4 mg/dl, eGFR from 75 to 68 at month 18). Serum creatinine values were evaluated according to DAIDS classification [16]: 56% patients had no renal impairment, 32% had mild impairment (serum creatinine values from 1.1 to 1.3 mg/dl), 12% had moderate impairment (from 1.4 to 1.8 mg/dl). Seventeen percent of patients improved to a lower serum creatinine class from baseline to month 18, while 2% worsened and 81% remained in the same class. According to KDIGO eGFR classification [14], 87% patients were classified into stage 1 or 2. 20% patients improved their stage of renal function and 44% patients remained in the same stage.

Regarding lipids, increases of both total cholesterol [from 188 mg/dl (SD: 42) to 206 mg/dl (SD: 44); p=0.001] and HDL fraction [from 46 mg/dl (SD: 14) to 54 mg/dl (SD: 19); p=0.015] were observed at month 18. An increase in triglycerides concentration was observed from baseline [from 162 mg/dl (SD: 144) to 214 mg/dl (SD: 109); p=0.027] (see per protocol analysis in Table 2). Also ITT analysis showed increases of both total cholesterol [from 187 mg/dl (SD: 43.69) to 203 mg/dl (SD: 44.10); p<0.001] and HDL fraction [from 46 mg/dl (SD: 15.49) to 52 mg/dl (SD: 17.13); p=0.002] at month 18. Even if ITT analysis did not show statistically significant differences in mean values of triglycerides, an increased value was observed from baseline [from 168 mg/dl (SD: 124.67) to 201 mg/dl (SD: 199.50); p=0.154] (Table 2).

DISCUSSION

Several studies analyzed the effects of switching from TDF/FTC to ABC/3TC and vice-versa [20 - 24]. In these studies, the nucleos(t)ide (N(t)RTI) backbone was combined with diverse drugs used as anchor. Consistently with these
results, we found that switching from TDF/FTC to ABC/3TC improved eGFR. This improvement was confirmed by downgrading the stage of kidney disease along the follow-up.

The originality of our work is that, in contrast to other studies, ATV/r was maintained, consistently with the treatment strategy applied in the ATLAS trial [12]. However, in this trial, ABC was not used. So, our results suggest that switching from TDF/FTC to ABC/3TC backbone could be of benefit, even if ATV/r was maintained as anchor drug.

Another new demonstration is that the apparent benefit from switching was found in patients with normal renal function or mild impairment at baseline, suggesting the opportunity of an early or proactive switch, to prevent further deterioration of kidney function. It has to be seen whether tenofovir alafenamide (TAF), a new oral prodrug of tenofovir, will provide similar effect in patients on TDF when combined with ATV/r or other potentially nephrotoxic drugs. Indeed, TAF has already shown a better profile in terms of bone and renal safety with respect to TDF in naïve patients without significant renal diseases and in experienced patients with renal impairment [25 - 27].

Table 2. Results of per protocol and intention to treat analyses at month 18.

| Variables                     | Per protocol analysis, n=76 | Intention to treat analysis, n=126 |
|-------------------------------|-----------------------------|-----------------------------------|
| Serum creatinine (mg/dl)      | Baseline mean (SD)          | Month 18 mean (SD)               | P-value | Mean difference (95% CI) | P-value | Mean difference (95% CI) | P-value |
| 1.06 (0.3)                    | 0.94 (0.2)                  | 0.001 -0.01** [-0.01 to 0.003]  | <0.001  | 1.08 (0.3)               | 0.95 (0.2)               | <0.001  | -0.01** [-0.01 to -0.003] | <0.001  |
| eGFR (ml/min/1.73m²)          | 86.8 (33)                   | 96.4 (37)                         | 0.002  | 0.41** [0.21 to 0.61]    | <0.001  | 86.9 (24)               | 95.8 (20)               | <0.001  | 0.42** [0.26 to 0.58]   | <0.001  |
| Total cholesterol (mg/dl)     | 188 (42)                    | 206 (44)                          | <0.001 | 0.86** [0.40 to 1.32]    | <0.001  | 187 (44)                | 203 (44)               | <0.001  | 0.71** [0.31 to 1.10]   | <0.001  |
| HDL cholesterol (mg/dl)       | 46 (14)                     | 54 (19)                           | 0.005  | 0.36** [0.13 to 0.59]    | 0.015   | 46 (15)                 | 52 (17)                | 0.002   | 0.28** [0.11 to 0.46]   | 0.002   |
| Triglycerides (mg/dl)         | 162 (144)                   | 214 (109)                         | 0.004  | 2.26** [0.26 to 4.25]    | 0.027   | 168 (125)               | 201 (199)               | 0.114   | 1.21** [-0.29 to 2.72]  | 0.154   |

S.D.: standard deviation, eGFR: estimated glomerular filtration rate

** Adjusted for age, CD4+T cell count and risk factor for HIV infection

A note of caution for the use of ABC is worth mentioning in patients with significant cardiovascular risk. In fact, observational studies [28 - 30] have suggested an increased risk of myocardial infarction associated with ABC. Even though this finding has not been confirmed by a collate analysis of randomized trials [31] and it may be influenced by a channelling bias (so the impact of ABC is reduced and may become non significant when adjusted for other variables, such as calenda year [30]), biological plausibility has recently been supported because ABC may increase platelet adhesion [32]. When we investigated the lipid profile to get some insights on modifications of the cardiovascular risk, we observed a statistically significant increase in both total cholesterol and HDL cholesterol at month 18. This finding is due to stopping TDF, as already demonstrated [12]. Therefore, the increase of total cholesterol was confirmed in presence of ABC, but the simultaneous increase in HDL fraction may compensate for a possible increased risk of cardiovascular events. Further studies are necessary to elucidate both the risk and underlying mechanisms of ABC for cardiovascular complications.

Results of this study were intrinsically limited by its observational nature, by the small sample of population analysed, by the short time of observation and by the absence of a group of control. In particular, it would be useful to evaluate renal impairment after the switch to ABC/3TC with a control group of patients that continued therapy with TDF and to collect more data about anthropometric and metabolic profiles at baseline, as well as a detailed analysis of renal function (excretion of urine protein and electrolytes, and other biomarkers such as neutrophil gelatinase associated lipocalin [33] and/or cystatine C [34]). Lastly, it is unclear if the observed effect is related to creatinine secretion inhibition or decreased eGFR. To answer to this question we need to interpret the trend of eGFR on TDF prior to the switch in light of tubular function. For example, if serum creatinine rises after starting TDF and then declines after stopping TDF (and there is no glycosuria or proteinuria during TDF use), this may address inhibition of creatinine secretion by the HAART regimen rather than impact on eGFR or direct nephrotoxicity. Unfortunately, a complete dataset to test this hypothesis appropriately was not available. A prospective analysis focused on this aspect is therefore necessary.
CONCLUSION

In conclusion, this study showed an improvement of renal function and after switching from TDF to an alternative regimen, notwithstanding ATV/r and ABC intake. The novelty of our findings was that improvement in eGFR was obtained even in patients with preserved renal function and in association with ATV/r, suggesting that a proactive switch of TDF would be indicated, especially at the first signs of renal impairment.

LIST OF ABBREVIATIONS

| Abbreviation | Description                                    |
|--------------|------------------------------------------------|
| ABC/3TC      | Abacavir/lamivudine                            |
| ATLAS        | ATazanavir and LAmivudine Simplification study  |
| ATV/r        | Atazanavir/ritonavir                           |
| CKD-EPI      | Chronic Kidney Disease-Epidemiology Collaboration |
| eGFR         | Estimated glomerular filtration rate           |
| HAART        | Highly active antiretroviral therapy           |
| HCV          | Hepatitis C virus                              |
| HCV-Ab       | HCV antibodies                                 |
| HDL          | High density lipoprotein                       |
| HIV          | Human immunodeficiency virus                   |
| IQR          | Interquartile range                            |
| ITT          | Intention to treat                             |
| MASTER       | Management of Standardized Evaluation of Retroviral HIV Infection |
| N(t)RTI      | Nucleos(t)ide drugs                            |
| SD           | Standard deviation                             |
| TDF/FTC      | Tenofovir/emtricitabine                        |

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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