Impact of TDF + PI/r on Renal Function in Sub-Saharan Africa (2LADY/ANRS 12169)

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Introduction

Currently, Tenofovir Disoproxil Fumarate (TDF) is the most widely used antiretroviral because of its efficacy on both HIV and hepatitis B infections, and its favorable resistance profile, safety and availability as a coformulation with other antiretroviral drugs in once-daily pills. TDF is a component of the WHO-recommended first-line non-nucleoside reverse-transcriptase inhibitor-based regimen and second-line protease-inhibitor (PI)-based combinations.

However, TDF has been associated with acute kidney injury, proximal tubular dysfunction and impaired glomerular filtration. Moreover, concomitant use of ritonavir, leading to a 20-30% increase in the TDF plasma concentration, probably worsens the impact of TDF [1].

Several studies in sub-Saharan African countries reported high prevalence of renal dysfunction in HIV-infected populations which may be partly related to a strong susceptibility to chronic kidney disease in African populations [2,3].

Objective

The aim was to evaluate the impact on renal function of two regimens including co-administration of TDF with PI/r compared to a regimen including PI/r without TDF in HIV-infected patients starting a second line ART and included in the 2LADY / ANRS 12169 trial (Cameroon, Burkina Faso, Senegal).

Methods

Study design - 2LADY / ANRS 12169 trial is a multicenter, randomized, open-label, phase III trial comparing three second line regimens.



Population - HIV-1-positive adults failing standard first line from Yaounde, Cameroon; Bobo Dioulasso, Burkina Faso and Dakar, Senegal.

Intervention:

- **TDF/FTC LPV/r** : tenofovir 300 mg/emtricitabine 200 mg (1 tablet per day) with co-formulated lopinavir 200 mg/ritonavir 50 mg 2 tablets twice a day.
- **ABC ddI LPV/r** : abacavir 600 mg with didanosine (250 or 400 mg based on body weight) once a day with co-formulated lopinavir 200 mg/ritonavir 50 mg 2 tablets twice a day.
- **TDF/FTC DRV/r** : tenofovir 300 mg/emtricitabine 200 mg (1 tablet per day) with darunavir 400 mg (2 tablets) boosted with ritonavir (100 mg tablet) all taken with food once a day.

Procedures and definitions - Follow-up visits, including clinical and biological evaluation, were scheduled at weeks 4, 12, 24, 36 and 48 and then every 6 months. Serum creatinine (Jaffé method) and dipstick proteinuria were assessed using blood and urine samples collected at baseline and at all follow-up visits.

Estimated glomerular filtration rate (**eGFR**) was determined using the re-expressed Modification of Diet in renal Disease (MDRD) for standardized serum creatinine.

Chronic kidney disease (**CKD**) was defined as eGFR below 60 ml/min/1.73m².

Proteinuria was defined as urine dipstick result ≥ 1+.

Analysis -The per protocol population was used in this analysis and included all visits until **18 months**. Patients with eGFR <60 or ≥ 200 ml/min/1.73m² at baseline were not included. Mean changes in eGFR in the three treatment groups were compared using multivariable regression analyses.

Ethics - Written informed consent was obtained from all patients. Study protocol was approved by the appropriate ethic committees and health authorities and were conducted in accordance with the Declaration of Helsinski and Good Clinical Practices.

References
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Results

Table 1. Baseline characteristics

	Total N = 442
Study site, n (%)	
Cameroon	294 (67)
Burkina Faso	90 (20)
Senegal	58 (13)
Female, n (%)	318 (72)
Mean age (SD), years	39 (10)
Median CD4 [IQR], cells/mm³	186 [91-290]
CD4 count < 200 cells/mm³, n (%)	243 (55)
Viral load ≥ 100,000 cp/ml, n (%)	119 (27)
Asymptomatic, n (%)	402 (91)
Median treatment [IQR], years	4.1 [2.7-5.7]
Mean weight (SD), kg	66 (12)
Hypertension, n (%)	29 (7)
Diabetes, n (%)	3 (<1)
Mean eGFR (SD) ml/min/1.73m²	110 (27)
eGFR < 90 ml/min/1.73m², n (%)	110 (25)
Proteinuria (≥1+), n (%)	53 (12)

SD, standard deviation; IQR, interquartile range; eGFR, estimated glomerular filtration rate

Figure 1. Evolution of mean eGFR with 95% confidence interval

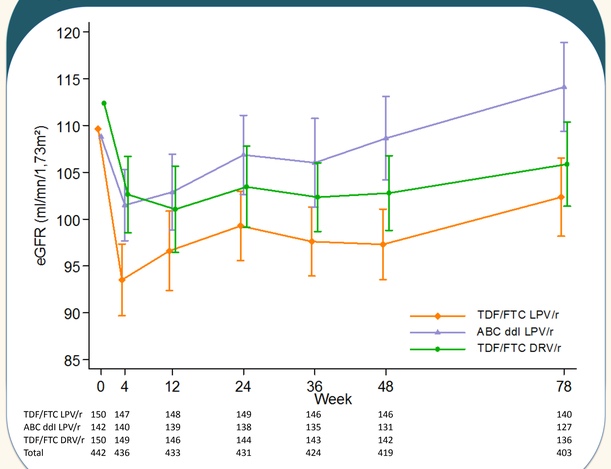
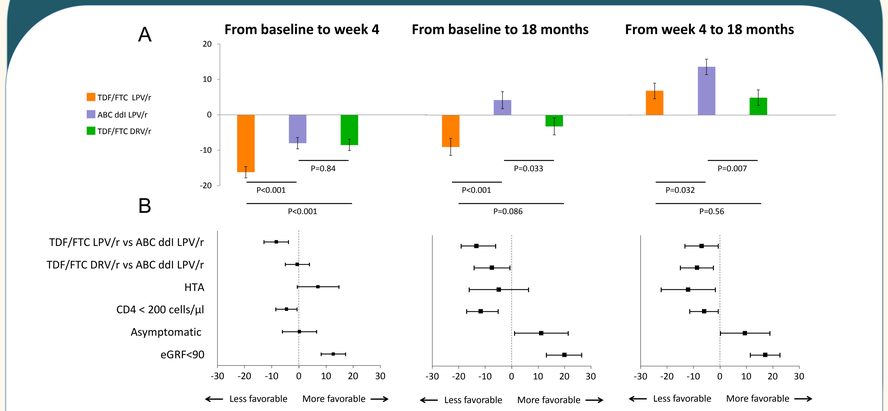


Table 2. Chronic kidney disease (CKD) and proteinuria

n (%)	TDF/FTC LPV/r	ABC ddI LPV/r	TDF/FTC DRV/r	P
CKD at 18 months	4 (3)	1 (<1)	2 (2)	0.41
Proteinuria at baseline	20/149 (13)	16/141 (11)	17/145 (12)	0.85
Proteinuria at 18 months	24/137 (18)	24/124 (19)	24/134 (18)	0.92

CKD was defined as eGFR < 60 ml/min/1.73m²; Proteinuria was defined as urine dipstick result ≥ 1+

Figure 2. Adjusted mean change in eGFR by treatment groups (A) and predictors of change in eGFR (B)



A: Adjusted mean eGFR changes (ml/min/1.73²) with standard errors. B: Regression coefficients for association with eGFR change (ml/min/1.73m²) and 95% confidence intervals.
All models are multivariable and include treatment group, study site, sex, age (years), weight (kg), viral load >100,000 copies/ml, CD4 count < 200 cells/µL, asymptomatic, treatment duration (years), eGFR < 90 ml/min/1.73m². Baseline values were considered with one exception : value at week 4 was considered for eGFR < 90 ml/min/1.73m² as a predictor of change from week 4 to 18 months. Although not shown, study site was associated with change in eGFR from baseline to week 4 and with change from week 4 to 18 months.

Out of 451 randomized patients, 442 were included in the analysis. Baseline characteristics were well balanced between treatment groups.

Evolution of estimated glomerular filtration rate (eGFR) (Figure 1 & 2)

The rate of decline of eGFR from baseline to week 4 was marked in all treatment groups with a greater mean decrease in TDF/FTC LPV/r than in ABC ddI LPV/r and TDF/FTC DRV/r groups. From week 4 to month 18, mean eGFR remained stable in TDF/FTC DRV/r and increased in the other two arms. The greatest increase was observed in ABC ddI LPV/r . At month 18, mean eGFR in the non-TDF containing regimen recovered its baseline level and was significantly greater than eGFR 18-month-levels in the TDF-containing regimens.

Predictors of change in eGFR (Figure 2B)

A CD4 count <200 cells/µL at baseline was associated with a less favorable evolution of eGFR whereas being asymptomatic at baseline was associated with a more favorable evolution.

Results also show improvement of eGFR among participants with eGFR < 90 ml/min/1.73m² at baseline or at week 4.

Prevalence of CKD and proteinuria at 18 months (Table 2)

A total of 7 participants had an eGFR <60 ml/min/1.73m² with no difference between treatment groups.

Prevalence of proteinuria increased from 12% at baseline to 18% at 18 months without any association with treatment. Only 6 participants with a pre-existing proteinuria at baseline, had higher grade of proteinuria at 18 months.

Two treatment discontinuations for renal toxicities were reported, one in TDF/FTC LPV/r and one in ABC ddI LPV/r.

Conclusions

Initiation of a second line regimen including ritonavir-boosted PI induced a marked decline in eGFR over the first month, followed by a recovery that differed according to treatment groups. Complete recovery at 18 months was observed in the ABC ddI group, whereas TDF/FTC PI/r regimen was associated with partial but substantial recovery.

The rate of renal events was low in all treatment groups.

These results suggest a good renal tolerance of the combination TDF/FTC + PI/r in African patients with eGFR > 60 ml/min/1.73m².

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