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Tenofovir Alafenamide, Emtricitabine, and Bictegravir in Switch Strategy for HIV-1 Adult Patients Due to Previous Renal Impairment Induced by Tenofovir Disoproxil Fumarate

R Correia de Abreu[1*], C Batista[2], S Caetano[3], Isabel Neves[1]

[1]Infectious Diseases Specialist/HIV Medical Researcher, ULS Matosinhos, EPE - Hospital Pedro Hispano, Matosinhos, Portugal

[2]Infectious Diseases Resident, ULS Matosinhos, EPE - Hospital Pedro Hispano, Matosinhos, Portugal

[3]Infectious Diseases Specialist, Associate Director, Medical Affairs, Gilead Sciences Portugal

[*]Correspondence should be addressed to Correia de Abreu R, rca.research@outlook.com

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Abstract

Introduction: Non-AIDS comorbidities, metabolic, renal and bone toxicities associated to combined antiretroviral therapy (cART), namely NRTIs, led to dual therapy (NUC sparing regimens). Tenofovir Alafenamide Fumarate (TAF) demonstrated improved renal and bone safety profile over TDF even with mild to moderate renal impairment.

Objectives: Evaluate if patients in NUCs sparing regimens due to previous TDF-induced renal impairment could switch to TAF/FTC/BIC, maintaining the safety renal profile.

Methods: Evaluate TAF/FTC/BIC renal parameters (estimated Glomerular Filtration Rate (eGFR) by CKD-EPI formula or Creatinine Clearence (CrCl) > 60 ml/min in 24h urine) at switch and week 4, 12, 24 and 48 and virologic suppression and lymphocytes T CD4$^+$ count. Discontinuation by any causes reported as failure.

Results: Fourteen patients, from 36-83 years old (average 61 y.o.), where 8 were females. The time of HIV infection range between 7-20 years (mean 14). And the major risk for HIV acquisition, was heterosexual in 9, drug addiction in 4 and "accidental" in 1 patient. At baseline, HIV RNA viral load was negative in 12, but in one 28 and another 103 cps/mL and the average lymphocytes T CD4$^+$ (CD4$^+$) count was 725 cells/uL (194-1516). According to CDC stage, 10 patients were in stage A and 4 at C at the switch.

Prior switch to TAF/FTC/BIC, 12 patients were on Raltegravir (RAL) + Etravirine (ETR) and Dolutegravir (DTG)/Rilpivirine (RPV) and Abacavir/Lamivudine/Dolutegravir (ABC/3tc/DTG) with 1 patient each. All participants presented normal CrCl before switching to TAF/FTC/BIC.

At 48 weeks, 12 patients maintained normal renal pattern, however 4 had negative variation due to decompensation of their chronic diseases. HIV RNA viral load was negative in 10 patients, and 1presented 43 and another 69 cps/mL; the average CD4$^+$ was 693 cells/uL (237-1476). No discontinuation was observed due to the patients maintain values of eGFR/CrCl>30 ml/min.

Conclusion: TAF/FTC/BIC is a valid treatment option for patients in NUCs sparing regimens due to TDF-induced renal toxicity after renal function normalization, demonstrating being safe and effective. However, further studies are need.

Nevertheless, and regarding patients with comorbidities, renal function recovered after the TDF-induced change is so fragile that these patients require special attention and monitoring.

Keywords: Tenofovir Alafenamide; Emtricitabine; Bictegravir; TAF/FTC/BIC; Tenofovir Disoproxil Fumarate; HIV-1

Introduction

Through 30 years of HIV infection, knowledge of HIV virus structure, mode of action and replication has led to great advances in the development of antiretroviral drugs. Since monotherapy with zidovudine (AZT) (NRTI) in 1987 [1], different treatment strategies were implemented until 1996 [2], when combined antiretroviral therapy (cART) of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NUCs) plus a third active drug from a different class [non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) [3] or, more recently, integrase strand transfer inhibitors (INSTIs)] was established. Today, INSTIs are recommended for initiation and maintenance therapy in guidelines [4-6] worldwide due to their high efficacy, especially when associated with Tenofovir disoproxil fumarate/Emtricitabine (TDF/FTC). However, renal and bone toxicity related to TDF has been a concern in the long-term management of HIV infection as a chronic condition.

Since the introduction of cART, stander of care (SOC) showed that 3 drugs enabled a more effective control of viral suppression, a more sustained recovering of the immune response and a decrease of resistance induction capacity so it became widely recommended by international guidelines [4-6]. Further studies with the combination of more than 3 drugs demonstrated no better efficacy results and worst safety profile, with more toxicity [7,8]. However, as previously presented, the development of non-AIDS comorbidities [9-11] (diabetes, arterial hypertension, dyslipidemia, cardiovascular events, etc.) and the onset of metabolic, renal and bone toxicities associated to cART, namely to NRTIs, led to new therapeutic strategies, such as NUCs sparing regimens. Although with limited data on this strategy, 2 drug combination (dual) therapies based on PI and INSTI were adopted in well-controlled and highly adherent patients to avoid toxicity, including TDF related renal impairment aside, clinically relevant drug-drug interactions with boosted agents [12].

Studies with dual therapies with PI and INSTI, provided insights into potential benefits of these regimens. ATLAS [13], DUAL [14] and SWORD [15] are examples of randomized controlled studies, and all demonstrated non-inferiority efficacy results. Nevertheless, these treatment strategies should be considered experimental [4-6] due to lack of sufficient data from randomized, appropriately powered clinical trials, well-matched and compared studies with SOC. Regarding the metabolic impact of TDF, Tenofovir alafenamide (TAF), a novel prodrug of TDF [21-23] that results in 80-90% lower plasma TDF levels, was developed, and demonstrated improved renal and bone safety profile in a broad population, including patients with mild to moderate renal impairment (eGFR - estimated Glomerular Filtration Rate (eGFR) by CKD-EPI formula or CrCl – Creatinine Clearance - in 24 h urine >30 ml/min). Nowadays, the combination TAF/FTC became a based regimen in clinical studies [24,25].

Bictegravir (BIC) is a novel once daily INSTI [26-28] that, as a single-tablet regimen (STR) [29] TAF/FTC/BIC, combines the potency and genetic barrier of BIC with the advantages of TAF [30] safety profile, overcoming safety previous limitations that led to alternative regimens [31,32]. However, this combination aside their proven benefit regarding renal impairment is not widely recommended for patients currently under treatment with dual therapy who had a recovery from renal and bone toxicity.

Objectives

Evaluate patients in alternative dual regimens due to previous renal impairment induced by TDF with proven recovery by normalization eGFR or CrCl >60 ml/min switch to TAF/FTC/BIC regarding renal function improvement (primary endpoint) and maintaining efficacy and safety profile through 48 weeks (secondary endpoint).

Methods/Study Design

Pilot, unmask, phase IV, single-arm, open label, switch study of adult HIV-1 infected patients with an undetectable plasma HIV-1 RNA for at least 6 months switch to TAF/FTC/BIC, after a full recovery of renal function (eGFR or CrCL > 60 ml/min) with NUC spearing regimen after renal dysfunction induced by TDF. The inclusion and exclusion criteria are presented in **Table 1**. Patients data were collected from medical charts at baseline and weeks 4, 12, 24 and 48 of follow-up. Most relevant data to be collected are presented in **Table 2**. Data collection

Table 1: Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
HIV-1 infected patients ≥ 18 years of age	HIV-1 patients with eGFR or CrCl <30 mg/dL at baseline and any study point
Patients in treatment with DRV/r + RAL or 3TC, ATV/r + RAL or 3TC, LPV/r + RAL or 3TC, RAL + ETR, ABC/3tc/DTG, DTG/RPV	A new AIDS-defining condition diagnosed within the 30 days prior to screening, or in treatment
Plasma HIV-1 RNA <50 copies/ml for at least 6 months; unconfirmed virologic evaluation of ≥ 50 copies/mL after previously reaching viral suppression (transient detectable viremia, or "blip") and prior to screening is acceptable	History of malignancy within the past 5 years (prior to screening) or ongoing malignancy other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma.

Proteinuria of any grade for at least 6 months when switched from TDF containing regimen to 2 drug combination+ eGFR <60 mg/dL (serious to moderate renal insufficiency) when switched to DUAL regimen+	Patients with any documented mutation associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir or previous virologic failure to any regimens containing INSTIs, FTC or TDF
Women of childbearing age should be abstinent, or, if sexually active, be practicing an effective method of birth control	Current alcohol or substance use judged by the investigator to potentially interfere with subject study compliance
An informed consent prior to inclusion was obtained	Active HCV and/or HBV coinfection
	Pregnant or nursing females.
	Subjects who are participating in an interventional study or who have taken any investigational drug in the last 30 days prior to screening
+KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3(1):2013.	

Table 2: Patients data collected.	
Socio-demographic	Date of birth, gender, race and ethnicity.
Clinical	Comorbidities (diabetes, arterial hypertension (HTN), dyslipidemia).
Antiretroviral therapy (cART)	Total cART duration; total number of previous regimens; last regimen of triple therapy and duration before switching to dual therapy; regimen of 2 drug combination therapy and duration at baseline.
All other medications	Namely for HTN, for diabetes and nephrotoxic.
Laboratory	eGFR (CKD-EPI formula), Serum Creatinine (SCr), CrCl, HIV-1 RNA viral load, CD4 cell count among others (biochemical profiles, hematologic counts); resistance test for all patients with virological failure.
Adverse Effects (AE)	Including those leading to discontinuation.

respected patients' confidentiality and no identifiable data was registered in the study case report form. Database was anonymized and only aggregated data presented in the study publication.

At the design of the study, several concerns were outlined and defined as primary and secondary endpoints, which are presented in **Table 3**. By study definition, any discontinuation by any causes (toxicity, miss doses, AE) reported as failure.

Sample size

Due to the nature of this study, no sample size was previously defined. The total of patients with inclusion criteria were 14

Table 3: Primary and secondary endpoints.	
Primary Endpoint	**Secondary Endpoint**
Patients with improved or maintained level of eGFR from baseline to week 48 (severity level: normal, mild, moderate, severe)+	Efficacy: Virologic response was determined using the percentages of subjects with HIV-1 RNA <50 copies/mL observed through Week 48 Safety: Defined according to severity level: normal, mild, moderate and severe. Safety evaluations include reporting of adverse events, clinical laboratory tests, physical examinations, and vital signs. Renal safety monitored by evaluating+: • Patients with improved or maintained level of eGFR from baseline to week 48 • Lipid profile monitored by evaluating values of triglycerides, total, LDL and HDL cholesterol at week 48. Tolerability: Discontinuation rate.
+KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3(1):2013.	

that voluntary agree to participate after full and detailed explanation and assent was obtained.

Results

Fourteen patients agreed to switch to the therapeutic regimen of dual therapy started after a decrease in eGFR <60 ml/min and which allowed the recovery to normal values of the eGFR to a single tablet regimen of TAF/FTC/BIC. The switch occurred between November 2019 and August 2020. The majority were female (8) with the ages ranging from 36 to 83 (62.14 ± 12.84) years old. Regarding the HIV *status*, the time of infection ranged from 7 to 20 (13.64 ± 3.52) years. The major risk was heterosexual infection in 9, drug addiction in 4 and "accidental" in 1. At baseline, the HIV RNA was negative in 12, one with 28 and other 103 copies/mL (cps/mL); the average $CD4^+$ count was 725 cells/uL (194-1516) and the staging was done according to the Centre for Disease and Prevention Control (CDC) criteria, 10 patients were at stage A (9 at stage A1 and 1 at A2); 4 were at stage C (2 at stage C1 and 1 at C2) when they were proposed to switch therapy.

Six patients had comorbidities, with more than one in the same patient. From those, was reported diabetes mellitus in 4, hypertension in 2, dyslipidemia in 5, thyroid disease in 1 and 1 patient had fully recovered from a non-Hodgkin lymphoma treated with chemotherapy 7 years ago. These patients were under medication to those comorbidities – statins, anti-hypertension drugs, levothyroxine and metformin. However, only <50% of the patients with diabetes, hypertension and dyslipidemia were controlled due to bad adhesion to prescription.

Prior to the switch to TAF/FTC/BIC, all patients were switched from previous antiretroviral therapy due to TDF-induced renal impairment, documented by creatinine clearance (CrCl) in urine of 24 h <60 ml/min to RAL+ETR (12 patients), 1 to DTG/RPV and another to ABC/3tc/DTG and these therapies had a follow-up time between 51-93 (80 ± 12) weeks. The major reason for switch to TAF/FTC/BIC was simplification in 12 and renal toxicity in both cases with DTG. The eGFR of the 14 patients at the time of switch was presented in **Table 4.**

The evolution of the patients regarding their HIV *status*, namely RNA HIV-1 and lymphocytes T $CD4^+$ count since the time of the switch through the 48 weeks of follow –up is listed in **Table 5**. It is important to say, that the RNA HIV-1 cut off was <50 cps/mL. As the evolution of the renal parameters is a concern, they are presented in the **Table 6**.

Considering TAF is associated to an increase in cholesterol levels, the variation of cholesterol levels was collected and the results are presented in **Table 7**.

Discussion

Regarding the lack or no data to the experience of treating patients with prior renal damage induced by TDF with TAF after renal recovering or stabilization, this pilot study permits to say that TAF/FTC/BIC is safe on the evaluated parameters of efficacy and security. During the 48 weeks, none of the patients in the study experience therapy failure, and only in two there was a "positive" viral load, both <100 cps/μL the rest had negative viral loads. The same was observed in the lymphocytes T $CD4^+$ count, where 2 patients were exception,

Table 4: eGFR and regimens prior to switch to TAF/FTC/BIC.

Patients	eGFR prior to dual therapy (mL/min)	Pre-TAF/FTC/BIC ARTc
1	32.4	RAL + ETR
2	55.7	RAL + ETR
3	60.2	RAL + ETR
4	42.32	ABC/3tc/DTG
5	55.4	RAL + ETR
6	65.15	RAL + ETR
7	59.07	RAL + ETR
8	48.2	RAL + ETR
9	54.4	RAL + ETR
10	48.5	RAL + ETR
11	55.1	RAL + ETR
12	65.7	RAL + ETR
13	56.05	RAL + ETR
14	58.9	DTG/RLP

Table 5: Evolution of the HIV *status* through the 48 weeks of the 14 patients.

Patients	HIV-1 RNA switch (cps/mL)	HIV-1 RNA 4 weeks (cps/mL)	HIV-1 RNA 24 weeks (cps/mL)	HIV-1 RNA 48 weeks (cps/mL)	Lymph. T $CD4^+$ switch (cells/µL)	Lymph T $CD4^+$ 4 weeks (cells/µL)	Lymph T $CD4^+$ 24 weeks (cells/µL)	Lymph. T $CD4^+$ 48 weeks (cells/µL)
1	0	0	n.d*	0	634	634	n.d*	521
2	0	n.d*	0	0	1202	n.d*	1075	1184
3	0	n.d*	0	0	935	n.d*	839	635
4	0	0	29	43	194	190	172	237
5	0	0	0	0	560	666	627	468
6	0	0	0	0	473	498	572	579
7	0	n.d*	0	0	478	n.d*	831	578
8	0	0	n.d*	0	1516	1176	n.d*	1476
9	28	0	0	0	699	706	607	720
10	0	n.d*	0	0	685	n.d*	625	432
11	0	0	0	0	1078	871	1272	825
12	0	n.d*	0	0	631	n.d*	693	739
13	0	n.d*	0	0	231	n.d*	263	461
14	104	39	69	69	829	707	734	841

n.d* - Not done due to laboratory difficulties

Table 6: Evolution of the renal parameters through the 48 weeks of the 14 patients.

Patients	SCr initial (mg/dL)	SCr 4 weeks (mg/dL)	SCr 24 weeks (mg/dL)	SCr 48 weeks (mg/dL)	eGFR initial (ml/min)	eGFR 4 weeks (ml/min)	eGFR 24 weeks (ml/min)	eGFR 48 weeks (ml/min)
1	1.1	1.1	n.d*	1.4	48.26	48.26	n.d*	39.93
2	0.9	n.d*	1	0.9	62.91	n.d*	58.63	66.78
3	0.9	n.d*	0.9	0.8	76.84	n.d*	77.39	85.14
4	1.2	1	1	0	46.47	63.50	60.73	55.23
5	0.8	0.8	1	11	75.13	71.78	58.78	64.48
6	0.9	1.3	1.2	2	59.36	38.21	43.81	23.46
7	1	n.d*	1.2	1.2	87.26	n.d*	67.84	68.06
8	1	1	n.d*	1	>90	>90	n.d*	>90
9	1.1	1.1	1.2	1.1	74	70.02	65.28	71.07
10	0.8	n.d*	0.8	0.9	84.3	n.d*	85.56	80.15
11	0.7	0.7	0.7	0.9	>90	>90	>90	71.21
12	1.1	n.d*	1	1	72.8		80.08	81.04
13	1.4	n.d*	1.4	1.4	53.3	n.d*	53.84	54.4
14	1.7	1.2	1.5	1.6	37.82	53.42	42.83	38.12

n.d* - Not done due to laboratory difficulties

Table 7: Evolution of the cholesterol parameters through the 48 weeks of the 14 patients.

Patients	Switch				48 Weeks				Variation (%)			
	Total Chol (mg/dL)	HDL Chol (mg/dL)	LDL Chol (mg/dL)	Trigl (mg/dL)	Total Chol (mg/dL)	HDL Chol (mg/dL))	LDL Chol (mg/dL)	Trigl (mg/dL)	Total Chol	HDL Chol	LDL Chol	Trigl.
1	229	41	145	236	135	36	78	166	-41%	-12%	-46%	-30%
2	161	76	62	117	157	46	81	229	-2%	-39%	31%	96%
3	149	22	92	328	158	23	121	170	6%	5%	32%	-48%
4	161	53	93	77	123	36	68	105	-24%	-32%	-27%	36%
5	188	95	80	67	205	81	98	91	9%	-15%	23%	36%
6	306	57	174	336	161	57	72	160	-47%	0%	-59%	-52%
7	150	44	72	172	168	39	112	148	12%	-11%	56%	-14%
8	160	52	93	73	117	41	64	72	-27%	-21%	-31%	-1%
9	141	51	66	119	165	36	96	163	17%	-29%	45%	37%
10	179	92	79	86	126	58	57	72	-30%	-37%	-28%	-16%
11	203	64	125	71	174	50	112	60	-14%	-22%	-10%	-15%
12	139	38	80	103	139	41	95	76	0%	8%	19%	-26%
13	118	47	51	85	131	37	72	123	11%	-21%	41%	45%
14	143	32	82	143	204	34	151	224	43%	6%	84%	57%

Legend: Chol: Cholesterol; Trigl: Triglycerides

one with 560 cells/µL at switch to 468 and another with 685 to 432 cells/µL, at the 48 weeks; in both the viral load was always negative.

While observing the evolution of the renal parameters through the 48 weeks of the 14 patients, all patients at 48 weeks presented a stabilization of the eGFR, presenting all >30 ml/min. Four (patients 1, 5, 6, 7) had a negative variation, understood as related due to non-controlled comorbidities, i.e., decompensated hypertension or diabetes already reported at the time of the switch. That conclusion was observed by the fact that was a positive response when those comorbidities were controlled *vs.* the time that they were non-controlled along the study. In one case, the aggravation of the eGFR was related to the fact that the patient was diagnosed with a prostatic infection due to *Klebsiella pneumonia* ESBL positive, that become a "chronic" infection. In fact, this is the oldest patient in this series with 83 years old. During the 48 weeks, no renal insufficiency was observed with need of switch or stopping ARV therapy in course.

To the fact that TAF is related to an increase of the dyslipidemia, in most patients no aggravation was observed after the switch to TAF/FTC/BIC. However, in two patients an anti-dyslipidemic therapy was needed to add to control the cholesterol LDL and the triglycerides, namely the patients 3 and 6. The patients that were already in anti-dyslipidemic therapy maintained the treatment without any report.

Conclusion

In conclusion, in this series, TAF/FTC/BIC demonstrated to be safe in patients with prior renal damage induced by TDF that had recovered or stabilized with previous dual therapy and no relapse of the renal function was observed. No major concerns were observed, regarding the efficacy and the tolerability of this scheme, like no major aggravation or decompensation of the cholesterol parameters during the 48 weeks. So, for patients currently under treatment with 2 drug combination regimens (NUC spearing regimes) to prevent or recover from renal toxicity, triple therapy with TAF/FTC/BIC should be considered as a valid treatment option, however, more studies are needed in this population to consider as a full recommendation to its use or even therapies with TAF.

Due to the risk of interference with the renal function, special attention is advised in patients with underlying non-AIDS comorbidities such as diabetes and arterial hypertension. In fact, renal function recovered after the TDF-induced change is so fragile that in patients with these comorbidities, even the smallest decompensation of those comorbidities, has a substantial impact in renal function. So the recommendation is that these patients always require special attention and monitoring.

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