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Tenofovir Alafenamide as Part of a Salvage Regimen in A Patient with Multi-Drug Resistant HIV and Tenofovir DF-Associated Renal Tubulopathy

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Brief Summary

We describe a patient with two recent episodes of tenofovir disoproxil fumarate (TDF)-associated acute kidney injury and six-class drug-resistant HIV infection who achieved and maintained viral suppression without worsening kidney function on a regimen including tenofovir alafenamide (TAF) through 48 weeks of therapy. The safety and efficacy of TAF in patients with TDF-associated renal tubulopathy and multiple drug resistance HIV has not yet been described. TAF may represent a useful option to maximally suppress HIV in patients with these complications.

Despite the success of potent combination antiretroviral therapy (ART), there is still a small but notable subset of patients who harbor HIV strains resistant to all antiretroviral drug classes and fail to achieve viral suppression. Some of these patients may have initiated on ART with sequential monotherapy and were treated with drugs that were less potent, more toxic, and had difficult dosing requirements that impacted adherence. This may lead to the accumulation of multiple drug class resistance leading to very limited treatment options.

Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor that remains an important agent for treatment-experienced patients. However, long-term use of TDF has been associated with renal tubulopathy and decreased bone mineral density (1-3). Moreover, TDF-associated resistance may emerge after long-term suboptimal therapy.

Tenofovir alafenamide (TAF) is a novel, investigational prodrug of tenofovir (TFV) that results in lower systemic TFV exposure and greater intracellular TFV concentration after oral administration compared to TDF (4). TAF has demonstrated potent antiviral activities when used in treatment-naïve patients in Phase 3 trials (5), and may alleviate renal and bone toxicities caused by TDF (6). Its role in patients with NRTI-resistance has not been explored. Dolutegravir is a second-generation HIV integrase strand transfer inhibitor with good activity against some HIV strains resistant to raltegravir and elvitegravir (7). We report a case of successful viral suppression with a TAF and dolutegravir-containing regimen in a patient with extensive multi-antiretroviral drug class resistance, with two prior episodes of acute kidney injury (AKI) while receiving TDF.

Case

The patient is a 54-year-old Caucasian man who was diagnosed with HIV-1 infection and *Pneumocystis pneumonia* in 1995. His CD4+ count was 16 cells/mm³. He underwent zidovudine monotherapy followed by dual NRTI therapy, and then combinations of at least three drugs. Over subsequent years, he achieved an HIV RNA level <50 copies/mL on only one occasion and had been treated with all approved antiretroviral drugs except dolutegravir, maraviroc, delavirdine and rilpivirine. His CD4+ count remained <200 cells/mm³ and <50 cells/mm³ since 2007. His medical history was notable for ART-related complications including peripheral neuropathy, severe lipodystrophy, and dyslipidemia. His comorbidities included basal and squamous cell carcinomas, hypertension, and obstructive sleep apnea. His concomitant medications included SMX/TMP, azithromycin, rosuvastatin, lisinopril, hydrochlorothiazide, temazepam, lorazepam, venlafaxine, testosterone, omega-3 fatty acids, and milk thistle. His physical examination was most notable for a large neck, small buffalo hump, central obesity and thin extremities.

In October 2013, two months after starting a regimen consisting of enfuvirtide and elvitegravir/cobicistat/TDF/emtricitabine (Figure 1), his serum creatinine increased from 1.47 mg/dL (130 µmol/L) to 4.55 mg/dL (402 µmol/L). Correspondingly, his estimated glomerular filtration rate (eGFR) by the CKD-EPI creatinine equation fell from 53 mL/min/1.73 m² to 14 mL/min/1.73 m². In the setting of presumed iatrogenic kidney injury, his ART and sulfamethoxazole/trimethoprim (SMX/TMP) were discontinued, which resulted in an improvement in SCr to 2.16 mg/dL (191 µmol/L, eGFR 34 mL/min/1.73 m²) in one month. He then restarted SMX/TMP and ART with raltegravir and renal dose-adjusted TDF 300 mg and emtricitabine 200 mg each taken every other day.

In April 2014, he presented to the National Institutes of Health for enrollment in a protocol aiming to manage patients with ART failure ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01976715) identifier NCT01976715). His laboratory results at presentation revealed SCr of 3.18 mg/dL (281 µmol/L, eGFR 21 mL/min/1.73 m²), CD4 count of 21 cells/mm³ (1%), and HIV RNA of 10,748 copies/mL. Due to his rising SCr, TDF, SMX/TMP, hydrochlorothiazide and lisinopril were discontinued, he received intravenous hydration, and his study enrollment was deferred. A summary of the genotypic and phenotypic resistance testing from this visit (Table 1) revealed resistance to all approved antiretroviral drugs except for sensitivity to dolutegravir (phenotypic IC₅₀ fold-change 2.02) and partial sensitivity to TDF (2.84 fold-change). Sanger

genotyping revealed NRTI mutations M184V, M41L, L210W, and T215Y, integrase mutation N155H and extensive PI resistance mutations including I47V, I54M, I84V and L90M. Phenotype reports showed resistance to all protease inhibitors, including darunavir (289 fold-change) and non-nucleoside reverse transcriptase inhibitors, and decreased susceptibility to enfuvirtide (28 fold-change). A co-receptor tropism test from 2013 revealed dual/mixed tropic virus.

On 1 July, 2014, after discontinuation of TDF and while on a regimen of only raltegravir and emtricitabine, his SCr decreased to 1.49 mg/dL (132 μ mol/L, eGFR 52 mL/min/1.73 m²) and his viral load increased by 0.57 log₁₀ to 39,950 copies/mL (Figure 2), suggesting that TDF was responsible for partial viral suppression. In an attempt to prevent further accumulation of integrase mutations, raltegravir was discontinued and replaced with ritonavir-boosted darunavir. In August 2014, given his limited treatment options, we obtained co-formulated TAF 25mg/emtricitabine 200mg (Gilead Sciences, Foster City, CA) through a single patient investigational new drug (IND 123392) with approval from the FDA. A regimen of TAF 25 mg/emtricitabine 200 mg once daily, dolutegravir 50 mg twice daily, and ritonavir-boosted darunavir (100 mg/600 mg) twice daily was initiated. At that time, his CD4⁺ count was 24 cells/mm³, HIV RNA was 47,538 copies/mL, SCr was 1.30 mg/dL (115 μ mol/L, eGFR 62 mL/min/1.73 m²), serum cystatin C was 1.37 mg/L (reference range 0.55 – 1.03 mg/L), urine albumin was 196 mg/L, and urine beta-2-microglobulin was >2.5 mg/L. After 2 weeks of the new ART regimen, his urine albumin was 182 mg/L, with a urine albumin to protein ratio (UAPR) of 19% and a urine albumin to creatinine ratio (UACR) of 122 mg/g. SMX/TMP was restarted at week 4. He achieved HIV RNA <40 copies/mL at week 8. At 15 months of follow-up, virological suppression was maintained, his CD4⁺ count increased to 66 cells/mm³, SCr remained stable at 1.41 mg/dL (125 μ mol/L), eGFR was 55 mL/min/1.73 m², cystatin C was 1.43 mg/L, urine beta-2-microglobulin remained at >2.5 mg/L, and urine albumin was 185 mg/L with a UAPR of 7% and a UACR of 95 mg/g. Dual-energy X-ray absorptiometry (DEXA) scans performed at 6 and 12 months of TAF therapy detected no change in bone mineral density (BMD) of hip and spine, compared to baseline

Discussion

Over 20 antiretroviral agents spanning six distinct mechanistic drug classes have been approved for clinical use. Clinical guidelines recommend managing treatment failure by including at least two, and preferably three, fully active agents in a salvage regimen (8). Two active agents, however, may not be available for patients with substantial treatment experience and mutations that confer cross-resistance to multiple antiretroviral drugs within a class.

Dolutegravir has not been shown to select for integrase inhibitor-resistant strains in treatment-naïve patients but is less active against strains with specific integrase mutations selected by raltegravir and elvitegravir (9, 10). In our patient, while awaiting approval of a single patient IND to use TAF, we discontinued raltegravir and initiated ritonavir-boosted darunavir to avoid emergence of additional integrase resistance mutations, particularly the

mutation at position Q148, which has been associated with virologic failure on optimized regimens (7, 10).

Our patient's phenotypic testing reported sensitivity to dolutegravir, but only partial to no susceptibility to the remaining components of his antiretroviral regimen, including substantial increases in IC₅₀ to TDF (2.84 fold, partial sensitivity from 1.4 to 4 fold-change), darunavir (289-fold) and emtricitabine (>max). The phenotype showed a lesser 15-fold change in susceptibility to saquinavir; however, we chose darunavir over saquinavir, as there is broad experience with darunavir in salvage therapy in clinical trials and in clinical practice (11). With dolutegravir and darunavir, higher doses and blood concentrations can increase antiretroviral activity against HIV strains with intermediate resistance to these drugs (12, 13). It is unknown if TFV exerts a similar dose-response effect. The history of AKI prohibited use of higher TDF doses; in contrast, TAF retains greater activity *in vitro* than TDF against partially sensitive HIV-1 strains on the basis of greater peripheral blood mononuclear cell (PBMC) TFV concentrations (1, 2, 14). Unlike TDF, after oral absorption, TAF is stable in plasma and mainly metabolized to the pharmacologically active TFV-diphosphate after reaching its site of action by intracellular uptake by CD4+ cells (15). Compared to TDF, TAF resulted in 90% lower serum concentration of TFV and 6-fold higher PBMC TFV concentration (16). While virologic potency of TAF in patients with TFV-associated resistance is yet to be defined *in vivo*, TAF 25 mg daily provided a significantly greater decrease in HIV RNA than TDF 300 mg (−1.46 versus −0.97 log₁₀ copies/mL, p=0.024) after 10 days of monotherapy in antiretroviral-naïve subjects (17). Our patient, taking TAF with only one fully active agent in dolutegravir, achieved a 1.6 log₁₀ decrease in HIV RNA after seven days, and a >3.1 log₁₀ decrease to <40 copies/mL by week 8, and maintained suppression through 48 weeks.

Two 48-week phase 3 studies of treatment-naïve subjects have demonstrated virologic non-inferiority and a favorable safety profile of TAF compared to TDF (5). Similarly, two randomized phase 3 studies of virologically suppressed subjects without kidney disease showed that subjects who switched from TDF to TAF had a higher rate of virologic suppression (97% to 93%, P<0.001), less proteinuria, and improvement in BMD after 48 weeks compared to subjects who continued on a TDF regimen (6), though DEXA scan detected no change in BMD of the hip and spine in our patient after 12 months of TAF. In a prospective cohort switch study of 242 virologically suppressed patients with mild to moderate renal dysfunction (Cockcroft-Gault eGFR of 30 to 69 ml/min), subjects who switched from TDF to TAF did not experience any change in Cockcroft-Gault eGFR and showed significantly reduced proteinuria by urine protein to creatinine ratio, UACR, urine beta-2-microglobulin and urine retinol-binding protein after 48 weeks (18). There are no published data on the tolerability of TAF in patients with previous AKI secondary to TDF, and it is unknown whether switching from TDF to TAF results in improvement of TDF-induced renal tubulopathy and proteinuria in these patients. Our patient continued to have stable moderate renal dysfunction with proteinuria during 12 months of TAF therapy. His UPCr, UACR and urine beta-2-microglobulin level continued to indicate tubulopathy, although glomerular disease secondary to hypertension could be contributory. As creatinine tubular secretion can be inhibited by dolutegravir (19), leading to falsely low eGFR calculations, we also monitored cystatin C concentration as another measure of renal

function. The utility of cystatin C as an independent marker of renal function in HIV-infected patients may be complicated, however, as it may be increased by HIV viremia and inflammation (20). Nonetheless, both eGFR and cystatin C remained stable throughout TAF and dolutegravir treatment in our patient, with no evidence of worsening renal function.

Current guidelines recommend discontinuing TDF in patients experiencing progressive GFR decline without other identifiable causes and avoiding TDF in patients with chronic kidney disease (21, 22). This may limit treatment options in some patients, particularly those with hepatitis B virus co-infection and those with extensively drug resistant HIV. We report here, in a single case, the ability to safely use TAF in a patient with TDF-associated kidney injury with proteinuria and severely impaired eGFR. Moreover, TAF, as part of a salvage regimen, was successful in achieving viral suppression in the setting of six-class antiretroviral drug resistance. The role of TAF in patients with TFV-associated resistance mutations and renal dysfunction warrants further study.

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Figure 1.

Antiretroviral regimens, serum creatinine, and cystatin-C prior to and after initiating a salvage regimen with tenofovir alafenamide

COBI = cobicistat, DRV/r = ritonavir-boosted darunavir, DTG = dolutegravir, EVG = elvitegravir, FTC = emtricitabine, RAL = raltegravir, SCr = serum creatinine, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, T20 = enfuvirtide

Figure 2.

Antiretroviral regimens, HIV viral load, and CD4+ cell count prior to and after initiating a salvage regimen with tenofovir alafenamide

COBI = cobicistat, DRV/r = ritonavir-boosted darunavir, DTG = dolutegravir, EVG = elvitegravir, FTC = emtricitabine, RAL = raltegravir, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, T20 = enfuvirtide

Table 1

Genotypic and Phenotypic Resistance Testing Reports

	Genotype ^a Resistance Mutations	Antiretroviral Drugs	Phenotype ^b Fold Change	Phenotype Report Interpretation
N(t)RTI	M41L, E44D, L74V, V118I, M184V, L210W, T215Y	Tenofovir^c	2.84	Partially sensitive
		Abacavir	12	
		Didanosine	2.76	
		Emtricitabine^c	>MAX	Resistant
		Lamivudine	>MAX	
		Stavudine	3.75	
		Zidovudine	168	
NNRTI	A98G, K101H, V108I, V179F, Y181C, G190A, H221Y, K238R	Efavirenz	>MAX	Resistant
		Etravirine	117	
		Nevirapine	>MAX	
		Rilpivirine	30	
PI	L10I, V11L, I13V, V32I, L33F, E34D, M36L, M46I, I47V, I54M, Q58E, D60E, A71V, I84V, L89I, L90M	Darunavir^c	289	Resistant
		Atazanavir	62	
		Fosamprenavir	>MAX	
		Indinavir	36	
		Lopinavir	>MAX	
		Nelfinavir	51	Resistant
		Ritonavir	>MAX	
		Saquinavir	15	
		Tipranavir	>MAX	
INSTI	V151I, N155H, E157Q	Dolutegravir^c	2.02	Sensitive
		Elvitegravir	132	Resistant
		Raltegravir	73	
CCR5 Inhibitors	N/A	Maraviroc	Dual/Mixed Tropic HIV	No activity anticipated
Entry Inhibitors	N/A	Enfuvirtide	28	Reduced susceptibility

Abbreviations: INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, N(t)RTI = nucleoside/nucleotide reverse transcriptase inhibitor, PI = protease inhibitor

^aTRUGENE® HIV-1 Genotyping Test - sample from April 22, 2014

^bPhenoSense GT Plus Integrase, Monogram Biosciences, South San Francisco, CA - sample from May 19 2014

^cBolded information represents the drugs prescribed as part of the salvage regimen in this patient