Factors Associated with Switching to Tenofovir Alafenamide when Care is Unrestricted

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Abstract

Background: Tenofovir alafenamide (TAF) is associated with fewer renal and bone toxicities than tenofovir disoproxil phosphate (TDF). Hence, most experts suggest switching to TAF. We examined factors associated with switching to TAF in the US Military HIV Natural History Study (NHS), a cohort of people living with HIV who have unrestricted access to care and medications.

Methods: The first formulation of TAF received FDA approval on 1 November 2015; hence, we included all NHS participants with visits between November 2015 and March 2019. Patient factors, including race, gender, CD4 count, antiretroviral therapies (ART), viral load, HIV diagnosis era and presence of comorbidities (cancer, heart disease, dyslipidemia, kidney disease and obesity), were assessed for association with a switch to TAF with a logistic regression model.

Results: Of the 1767 eligible participants, 1331 (75%) had received a TDF-based regimen. Participants who received a TDF-regimen were 94% male, 45% African-American [AA], 39% Caucasians and 17% Hispanic. About half the participants who received TDF-based ART switched to a TAF-based regimen (n=788, 59%). Of the 424 (32%) participants receiving TDF/FTC co-formulated with efavirenz, 57% (n=242) switched to TAF. The proportions switching to TAF were higher in those receiving TDF/FTC co-formulated with rilpivirine [68%, n=106] or elvitegravir/cobicistat [75%, n=165]. The common ART regimens after the switch were TAF co-formulated with elvitegravir/cobicistat (42%), bictegravir (20%), rilpivirine (15%) or and TAF/FTC combined with dolutegravir (14%). In an adjusted analysis, older participants, and participants receiving TDF/FTC in combination with efavirenz, dolutegravir, raltegravir, boosted protease inhibitors or a combination of boosted protease inhibitors and integrase inhibitors (other) were less likely to switch.

Conclusions: Despite the unrestricted access to care and ART in the NHS, only half of the participants switched to TAF. Participants on efavirenz-containing regimens were less likely to switch to a TAF-based regimen, possibly due to the lack of a co-formulated single tablet. These trends need to be followed and barriers to switching to TAF (both patient and provider) need examination.s

Background

- The availability of combination antiretroviral therapy (cART) has transformed HIV from a disease associated with an inexorable clinical course to one that is easily managed; the average life expectancy of an HIV+ individual is not dissimilar from an HIV- individual
- The care of the infected person focuses on optimizing cART i.e. choosing the regimen with the least toxicity, lowest pill burden, and avoiding drug-drug interactions) and reducing morbidity due to non-AIDS related conditions such as kidney, bone and liver diseases
- Tenofovir disoproxil fumarate (TDF) is a nucleoside reverse transcriptase inhibitor that is highly potent and generally well-tolerated. TDF forms the backbone of many modern cART regimens. However, TDF use is associated with both renal and bone toxicity which appears to be correlated with the plasma levels of the drug
- In 2015, tenofovir alafenamide (TAF), a new tenofovir pro-drug, was approved by the FDA. In comparison with TDF, TAF achieves higher intracellular level and lower plasma levels, and hence is associated with less renal and bone toxicities than TDF
- However, recent studies increases in lipids and body mass index (BMI) associated with TAF use
- In this study, we used data from a racially diverse cohort with HIV to assess the proportion of patients switching to TAF-based regimens from TDF-based regimens and factors associated with switching to TAF-based regimens

Methods

- The US Military HIV Natural History Study (NHS) cohort is comprised of HIV+ Department of Defense beneficiaries with open access to care and medications
  - Laboratory evaluations and physician examinations every six months
- Participants with follow-up visits starting November 2015 were eligible
  - Only included patients switching from TDF to TAF-based regimens
- Compared demographic, HIV-specific factors, and laboratory values
- Multivariate logistic regression analysis used to examine factors associated with switching to TAF

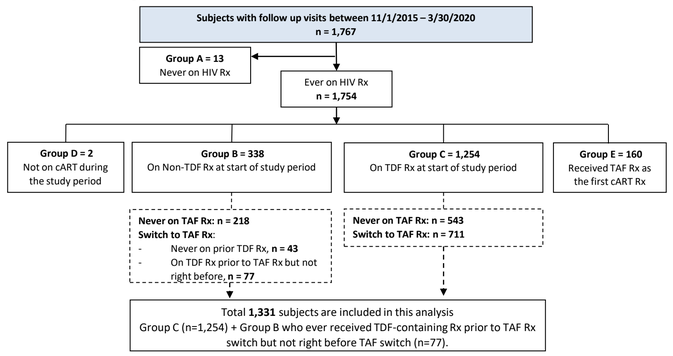

Figure 1: Flow Chart Depicting Subject Selection

Results

- A total of 1767 subjects had follow-up visits after January 1, 2016
  - 71% (n=1254) were receiving TDF-based cART prior to switch
  - 77 additional subjects who switched to TAF had been on TDF previously but not immediately prior to switch (**Figure 1**)
- Study population was mostly male (94%) and racially/ethnically diverse (45% African-American, 17% Hispanic) (**Table 1**)

Variable	Switch to TAF n(%)	Remain on TDF n(%)	Total N(%)	P
No. of Subjects	788 (59.2%)	543 (40.8%)	1331	.
Demographic Variables				
Gender				0.8556
Male	742(94.16)(59.27)	510(93.92)	1252(94.06)	
Female	46(5.84)	33(6.08)	79(5.94)	
Race				0.3221
Caucasian	305(38.71)	209(38.49)	514(38.62)	
African American	340(43.15)	252(46.41)	592(44.48)	
Hispanic	141(17.89)	82(15.10)	223(16.75)	
Missing	2(0.25)	0(0.00)(0.00)	2(0.15)	
Age at HIV Dx (y)	30.01[25.1-36.49]	28.77[24.4-35.24]	29.27[24.9-36.09]	0.0309
Age at ART initiation (y)	34.29[28.0-40.38]	32.89[27.2-40.15]	33.93[27.7-40.34]	0.1633
Service				0.0465
Army	221(28.05)	120(22.10)	341(25.62)	
Navy	325(41.24)	227(41.80)	552(41.47)	
Air force	167(21.19)	130(23.94)	297(22.31)	
Marines	50(6.35)	51(9.39)	101(7.59)	
Other Service	25(3.17)	15(2.76)	40(3.01)	
HIV-specific Factors				
cART Initiation Era				0.0440
Prior to 2000	241(30.58)	194(35.73)	435(32.68)	
Later 2000	547(69.42)	347(63.90)	894(67.17)	
On TDF at first cART Rx				0.3630
No	337(42.77)	245(45.12)	582(43.73)	
Yes	451(57.23)	296(54.51)	747(56.12)	
Time from HIV dx to AI (y)	1.09[0.2-5.38]	1.51[0.2-6.55]	1.26[0.2-5.86]	0.2009
Laboratory – HIV related				
CD4 at TDF Rx (cells/ul)*	698.00[554.0-895.0]	739.00[555.0-937.0]	716.00[554.0-913.0]	0.1402
CD4 at TDF Rx (cells/ul)*				0.3999
0-200	13(1.65)	9(1.66)	22(1.65)	
201-350	36(4.57)	37(6.81)	73(5.48)	
351-500	84(10.66)	59(10.87)	143(10.74)	
500+	621(78.81)	422(77.72)	1043(78.36)	
Missing	34(4.31)	16(2.95)	50(3.76)	
VL at TDF Rx (copies/mL)*				0.2666
0-200	739(93.78)	507(93.37)	1246(93.61)	
200+ - 100,000	17(2.16)	19(3.50)	36(2.70)	
100,000+	2(0.25)	3(0.55)	5(0.38)	
Missing	30(3.81)	14(2.58)	44(3.31)	
log(VL) at TDF Rx	1.30[1.3-1.3]	1.30[1.3-1.3]	1.30[1.3-1.3]	0.3820
Laboratory - Lipid Profiles				
Total Cholesterol at TDF Rx*	173.00[152.0-197.0]	175.00[148.0-198.0]	173.00[151.0-197.0]	0.9563
HDL at TDF Rx*	46.00[38.0-56.0]	45.00[37.0-55.0]	45.00[37.0-55.0]	0.4456
LDL at TDF Rx*	104.00[85.0-125.0]	104.00[79.0-125.0]	104.00[82.0-125.0]	0.2500
Glucose at TDF Rx*	97.00[89.0-106.0]	96.00[88.5-106.0]	96.00[89.0-106.0]	0.5972
Triglyceride at TDF Rx*	117.50[84.0-175.0]	122.00[82.0-192.0]	119.00[84.0-179.0]	0.4987
Comorbidities				
Had Chronic HepB prior to TAF Rx ever**				0.1062
No	738(93.65)	522(96.13)	1260(94.67)	
Yes	44(5.58)	20(3.68)	64(4.81)	
GFR at TDF Rx*				0.0112
Less than 60 (%)	65(8.25)	69(12.71)	134(10.07)	
60+ (%)	686(87.06)	459(84.53)	1145(86.03)	
Others				
Prior TDF Rx type				<.0001
EFV/TDF/FTC	242(30.71)	182(33.52)	424(31.86)	
RPV/TDF/FTC	106(13.45)	49(9.02)	155(11.65)	
EVG/COBI/TDF/FTC	165(20.94)	55(10.13)	220(16.53)	
TDF/FTC + RAL	34(4.31)	19(3.50)	53(3.98)	
TDF/FTC + DTG	94(11.93)	75(13.81)	169(12.70)	
TDF/FTC + ATV/r	44(5.58)	42(7.73)	86(6.46)	
TDF/FTC + DRV/r	42(5.33)	38(7.00)	80(6.01)	
Other	61(7.74)	83(15.29)	144(10.82)	

Note: The latest TDF Rx and the TDF Rx right before switching to TAF were considered for "Remain on TDF" and "Switch to TAF", respectively.
* For "Remain on TDF", we evaluated the measurements nearest to the most recent TDF Rx. For "Switch to TAF", we evaluated the measurements before switching to TAF Rx.
** For "Remain on TDF", we evaluated chronic Hep B occurred at any time (from HIV dx date to last visit date or 3/30/2020). For "Switch to TAF", comorbidities before switching to TAF were only considered.

Table 1: Baseline Characteristics and Other Measurements Based on Treatment Group

Results (cont.)

- Most participants on TDF were receiving TDF in combination with efavirenz (32%) or elvitegravir (17%) (**Figure 2A**)
- Most participants switched to TAF in combination with either elvitegravir (42%) or bictegravir (20%) (**Figure 2B**)

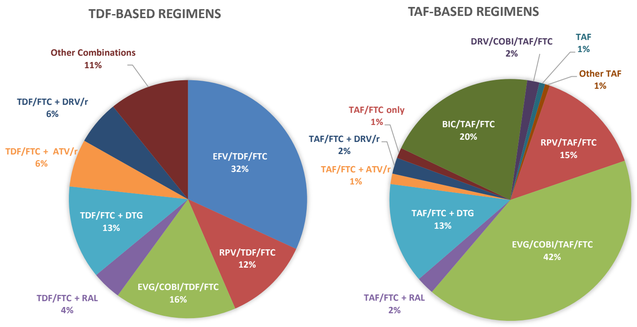

Figure 2: Breakdown of A) TDF-based Regimens and B) TAF-based Regimens

- The regimen with the highest proportion of switching to TAF was TDF in combination with elvitegravir and cobicistat; 75% of those on this regimen switched to a TAF-based regimen (**Figure 3**)

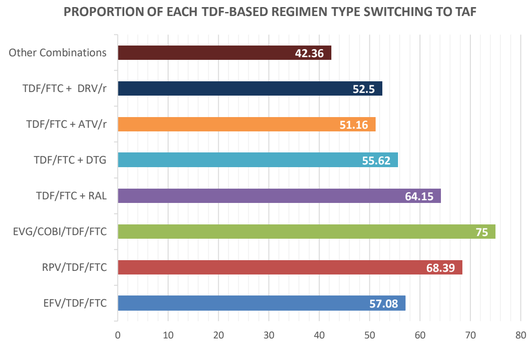

Figure 3: Proportion of Each TDF-based Regimen Type Switching to TAF

- Factors associated with switching to TAF include regimen type, service affiliation, GFR, history of hepatitis B, and regimen type (**Table 2**)

	Adjusted Model	
	OR (95% CI)	P
Age at HIV Dx (year)	1.00(0.97-1.03)	0.8610
Age at AI (year)	1.02(0.99-1.05)	0.2229
Service (vs. Army)		
Navy and Marine	0.79(0.59-1.05)	0.1089
Air Force	0.67(0.48-0.94)	0.0216
Other	0.82(0.40-1.66)	0.5736
cART era later 2000 (vs. prior to 2000)	0.98(0.74-1.30)	0.8946
CD4 at TDF (per 100 cells/ul)	1.00(0.99-1.00)	0.1765
Had Chronic HepB prior to TAF Rx/ever	2.13(1.18-3.86)	0.0125
GFR at TDF Rx 60+ (vs. <60)	1.62(1.10-2.41)	0.0159
TDF Regimen type (vs. Stribild)		
EFV/TDF/FTC	0.44(0.30-0.63)	<.0001
RPV/TDF/FTC	0.75(0.47-1.20)	0.2243
Other	0.21(0.13-0.35)	<.0001
TDF/FTC +InSTI	0.48(0.31-0.73)	0.0007
TDF/FTC +PI/r	0.35(0.22-0.56)	<.0001

Table 2: Adjusted Odds Ratio for Switching from TDF Rx to TAF Rx

Discussion

Since the introduction of TAF, 59% of the NHS participants on a TDF-based regimen switched to a TAF-based regimen. These numbers are similar to those in the Swiss Cohort Study, where 56% of those on TDF-containing ART switched.

Although prior studies have shown that racial minorities are less likely to initiate cART and achieve suppression, we found that racial minorities were as likely to be switched to a TAF-based regimen as Caucasians.

About 1 in 10 NHS participants had an eGFR<60 ml/min. Contrary to our expectations, these subjects were less likely to be switched to a TAF-based regimen. Future studies are needed to identify barriers to switching to TAF-based (or non-tenofovir) regimens in those with reduced renal function.

An important predictor of staying on TDF was the use of TDF in combination with efavirenz. It is possible that these patients may not experience CNS-related side effects to a degree that would prompt discontinuation of a well-tolerated regimen and switch to TAF, similar to results of the Swiss HIV Cohort Study.

Conclusions

A large number of NHS participants have switched to TAF-based regimens; the single most important factor associated with remaining on TDF appears to be the cART regimen type. Those on efavirenz-based regimens appear less likely to switch.

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