Prescribing rates and characteristics of recipients of tenofovir-containing regimens before and after market entry of tenofovir alafenamide

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What is already known about this subject

- Tenofovir disoproxil fumarate (TDF), one of the most widely used antiretroviral drugs since its approval in 2001, has been implicated in kidney injury and loss of bone mineral density.
- In clinical trials, tenofovir alafenamide (TAF) demonstrated favorable outcomes related to kidney injury and loss of bone mineral density, but increased lipid levels compared with TDF.
- Whether the favorable short-term endpoints assessed in these clinical trials outweigh any negative lipid effects and lead to favorable long-term outcomes is currently unknown.

What this study adds

- Approximately 2.5 years after approval, TAF prescribing rates had increased to match TDF prescribing rates in a large academic health system.
- Compared with TDF, TAF was more likely to be newly prescribed to patients with comorbidities, such as chronic kidney disease, as well as hyperlipidemia and cardiovascular disease.

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ABSTRACT

BACKGROUND: Tenofovir alafenamide (TAF) is a new formulation of tenofovir disoproxil fumarate (TDF) that was approved in 2015. While clinical trial evidence suggests that TAF has more favorable outcomes related to kidney injury and loss of bone mineral density, TAF also leads to higher lipid levels compared with TDF.

OBJECTIVES: To (a) determine prescribing rates of TDF and TAF among new recipients from 2014 to 2018 in a large academic health system and (b) compare baseline patient

characteristics of those newly prescribed TDF versus TAF before and after the approval of TAF in November 2015.

METHODS: Electronic health record data were used to identify new recipients of TDF or TAF from 2014 to 2018 and describe their total monthly TDF and TAF prescriptions by indication. Patient characteristics were compared among new recipients of TDF before November 2015, new recipients of TDF after November 2015, and new recipients of TAF.

RESULTS: Monthly TAF prescribing rates increased to match TDF prescribing rates by April 2018 (82 vs. 88 prescriptions per month).

TAF recipients and new recipients of TDF before November 2015 had similar racial distributions; both of these groups were more likely to be Black compared with new recipients of TDF after November 2015 (55% and 53% vs. 37%; $P < 0.0001$). TAF recipients also tended to have more comorbidities, including chronic kidney disease (7% vs. 2% and 2%; $P < 0.0001$), hepatitis C virus (8% vs. 5% and 3%; $P < 0.0001$), diabetes (13% vs. 5% and 6%; $P < 0.0001$), hypertension (27% vs. 13% and 13%; $P < 0.0001$), coronary artery disease (5% vs. 3% and 2%; $P < 0.0001$), hyperlipidemia (21% vs. 6% and 7%; $P < 0.0001$), and

congestive heart failure (3% vs. 1% and 1%; $P < 0.0001$), compared with both new recipients of TDF before and after November 2015.

CONCLUSIONS: TAF prescribing rates grew substantially in the 2.5 years after FDA approval. TAF is being prescribed more often than TDF in patients with chronic kidney disease and in patients with cardiovascular disease, suggesting that prescribers may be prioritizing the kidney safety profile over the effect on lipids.

Human immunodeficiency virus (HIV) infection is associated with an increased risk of chronic kidney disease.¹⁻⁴ Tenofovir disoproxil fumarate (TDF), one of the most widely used antiretroviral drugs since its approval in 2001, has been implicated in kidney injury and loss of bone mineral density.^{1,5-7} In addition to HIV treatment, TDF-containing regimens are approved for HIV pre-exposure prophylaxis (PrEP), HIV postexposure prophylaxis (PEP), and treatment of chronic hepatitis B virus (HBV) or HIV/HBV coinfection.

In November 2015, the U.S. Food and Drug Administration (FDA) approved a new formulation, tenofovir alafenamide (TAF), for use in the treatment of HIV, HBV, and HIV/HBV coinfection.⁸ In clinical trials, TAF led to smaller decreases in estimated glomerular filtration rate, less proteinuria and albuminuria, smaller decreases in bone mineral density in the spine, and increased bone mineral density in treatment-experienced patients switching from a TDF- to a TAF-containing regimen.⁹⁻¹⁹ However, increases in low-density lipoprotein and triglycerides were greater in patients treated with TAF than in those treated with TDF.⁹⁻¹⁹ Whether the favorable short-term endpoints assessed in these clinical trials outweigh any negative lipid effects and lead to favorable long-term outcomes is currently unknown. In the midst of this uncertainty, an assessment of clinician-prescribing patterns for TAF and TDF may inform future comparative effectiveness studies.

The primary objective of this study was to determine prescribing rates of TDF- and TAF-containing regimens among new recipients from 2014 to 2018 in the Duke University Health System. The secondary objective was to compare baseline patient characteristics of those newly prescribed TDF- versus TAF-containing regimens before and after November 2015.

Methods

STUDY POPULATION

New recipients of TDF or TAF between January 2014 and December 2018 in the Duke University Health System

(DUHS) were identified. DUHS is located in Durham, NC, and consists of 3 acute care hospitals, as well as multiple ambulatory primary care and specialty clinics. DUHS electronic health record data, which contain clinical, billing, and demographic information, were extracted using a web-based tool called the Duke Enterprise Data Unified Content Explorer.²⁰ To ensure new use of TDF, a 1-year lookback period was used, and patients with TDF use before 2014 were excluded.

TREATMENT INDICATION FOR EACH PRESCRIPTION

Total monthly prescriptions for any TDF- or TAF-containing medication ([Supplementary Table 1](#), available in online article) were extracted for the study cohort from January 2014 to December 2018. For each prescription, TDF or TAF was classified as used for HIV treatment if in the year before the prescription there was either an encounter with a relevant diagnosis code for HIV treatment ([Supplementary Table 2](#), available in online article) or the patient had been prescribed at least 3 antiretroviral medications. In accordance with labeling, TDF prescriptions could also be for HIV PrEP or PEP. Thus, if the TDF prescription was not determined to be used for HIV treatment and there was evidence of use in combination with emtricitabine (FTC) for more than 30 days, then the indication was classified as HIV PrEP.

Alternatively, if the patient had been prescribed TDF and FTC for less than 30 days, this prescription was determined to be for HIV PEP ([Supplementary Figure 1](#), available in online article). TAF was not approved by the FDA for use as PrEP during the study period. Use of TDF or TAF for HBV treatment was determined based on the presence of at least 1 encounter with a relevant diagnosis code ([Supplementary Table 2](#), available in online article) in the year before the prescription.

DEMOGRAPHICS AND COMORBIDITIES

Demographics and comorbidities were measured at first use of TDF or TAF. Comorbidities were defined based on the patient having at least 1 relevant diagnosis or procedure code ([Supplementary Table 2](#), available in online article) in the year before first use of TDF or TAF.

STATISTICAL ANALYSIS

The number of TDF and TAF prescriptions prescribed every month from January 2014 to December 2018 among new recipients of TDF and TAF was reported. The number of prescriptions was stratified by use for HIV treatment, HIV PrEP, HIV PEP, and/or HBV treatment. Demographics and comorbidities were compared between new recipients of TDF before November 2015 (when TAF was approved), new

FIGURE 1 Number of TDF and TAF Prescriptions by Month from 2014 to 2018^a

^aMono-HBV treatment and cotreatment of HIV and HBV not shown due to small numbers.

HBV = hepatitis B virus; PEP = postexposure prophylaxis; PrEP = pre-exposure prophylaxis; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; Tx = treatment.

recipients of TDF on or after November 2015, and new recipients of TAF on or after November 2015. Use of TAF before November 2015 was assumed to occur within the context of a clinical trial and was not included in this analysis.

Chi-square tests and Fisher's exact test were used to compare user groups. All tests were 2-sided, and a P value of <0.05 was considered statistically significant. All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC). This study was approved by the Duke University Health System Institutional Review Board.

Results

We identified 4,238 patients who were prescribed TDF or TAF between 2014 and 2018. Of these, 714 patients had initially been prescribed TDF before 2014 and were

thus excluded from analyses. Therefore, our final cohort included 3,524 patients.

MONTHLY PRESCRIBING RATES

In the study cohort, TDF prescribing increased from 55 prescriptions per month in January 2014 to 88 prescriptions per month in December 2018 (Figure 1). Over the study period, the proportion of TDF prescriptions for HIV treatment decreased (63% in January 2014 to 15% in December 2018) as the proportion for HIV PrEP increased substantially (6% in January 2014 to 67% in December 2018). The proportion of TDF prescriptions for HIV PEP remained relatively constant (16% in January 2014 to 11% in December 2018). Meanwhile, TAF prescriptions emerged in April 2016 (5 months after FDA approval) and increased to levels close to that of TDF by April 2018 (82 prescriptions per month). The majority of TAF prescriptions were written for HIV treatment alone. For TDF

TABLE 1 Characteristics of New Recipients of TDF vs. TAF

Demographics, n (%)	Before November 1, 2015	On or After November 1, 2015		P Value
	New Recipient of TDF (n=880)	New Recipient of TDF (n=1,778)	New User of TAF (n=866)	
Age, years				
0-18	34 (4)	115 (6)	4 (0.5)	<0.0001
19-30	223 (25)	674 (38)	112 (13)	
30-45	297 (34)	511 (29)	222 (26)	
45-64	298 (34)	427 (24)	435 (50)	
65+	28 (3)	51 (3)	93 (11)	
Sex				
Female	324 (37)	572 (32)	268 (31)	0.0183
Race				
White	277 (31)	763 (43)	257 (30)	<0.0001
Black	469 (53)	666 (37)	478 (55)	
Other	111 (13)	272 (15)	107 (12)	
Unknown	23 (3)	77 (4)	24 (3)	
Ethnicity				
Hispanic	56 (6)	140 (8)	48 (6)	0.0752
Not Hispanic	793 (90)	1,557 (88)	788 (91)	
Unknown	31 (4)	81 (5)	30 (3)	
Marital status				
Married	144 (16)	331 (19)	214 (25)	<0.0001
Single	561 (64)	1,139 (64)	483 (56)	
Other	94 (11)	136 (8)	99 (11)	
Unknown	81 (9)	172 (10)	70 (8)	

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and TAF prescribing, use for treatment of HBV mono-infection was low (median of 8% of TDF prescriptions and 12% of TAF prescriptions per month).

PATIENT DEMOGRAPHICS AND COMORBIDITIES

TAF recipients tended to be older (66% of TAF recipients were aged 45 years and above vs. 27% and 37% of new recipients of TDF before and after November 2015, respectively; $P<0.0001$) and were more likely to be male (69% vs. 68% and 63%; $P=0.0183$) and married (25% vs. 19% and 16%; $P<0.0001$)

than new recipients of TDF before or after November 2015 (Table 1). TAF recipients and new recipients of TDF before November 2015 had similar racial distributions; both of these groups were more likely to be Black compared with new recipients of TDF after November 2015 (55% and 53% vs. 37%; $P<0.0001$).

TAF recipients were more likely being treated for HIV treatment alone (82% vs. 51% or 21%; $P<0.0001$), cotreatment of HIV and HBV (4% vs. 1% or 0.3%; $P<0.0001$), and HBV treatment alone (12% vs. 5% or

7%; $P<0.0001$) compared with TDF recipients starting before or after November 2015. TDF recipients starting after November 2015 were more likely to use TDF for HIV PrEP (37% vs. 14%; $P<0.0001$) or PEP (27% vs. 18%; $P<0.0001$) compared with TDF recipients starting before November 2015.

New recipients of TAF also tended to have more comorbidities, including chronic kidney disease (7% vs. 2% and 2%; $P<0.0001$), hepatitis C virus (8% vs. 5% and 3%; $P<0.0001$), diabetes (13% vs. 5% and 6%; $P<0.0001$), hypertension (27% vs. 13% and 13%; $P<0.0001$), coronary artery disease (5% vs. 3% and 2%; $P<0.0001$), hyperlipidemia (21% vs. 6% and 7%; $P<0.0001$), and congestive heart failure (3% vs. 1% and 1%; $P<0.0001$), compared with new recipients of TDF before and after November 2015. Documented diagnosis of osteoporosis was rare, and although it was more common in new TAF recipients, there was no statistically significant difference between the groups (1% vs. 0.2% and 0.5%; $P=0.2204$).

Discussion

In this study, TAF prescribing rates increased to levels similar to that of TDF prescribing rates approximately 2.5 years after FDA approval. To our knowledge, this is the first study to examine TDF and TAF monthly prescribing patterns in a U.S. health system. Although a generic version of the single-agent TDF drug product was made available in December 2017,²¹ no substantial increase in TDF prescribing rates was seen after December 2017.

This study found prescribing differences by race and comorbidity. After TAF entered the market, we found that prescribers were more likely to prescribe TAF than TDF in Black populations. This may be due to clinicians prescribing TAF to patients with comorbidities such as chronic

TABLE 1 Characteristics of New Recipients of TDF vs. TAF (*continued*)

Demographics, n (%)	Before November 1, 2015	On or After November 1, 2015		P Value
	New Recipient of TDF (n=880)	New Recipient of TDF (n=1,778)	New User of TAF (n=866)	
Treatment indication, n (%)				
HIV Tx only	449 (51)	365 (21)	706 (82)	<0.0001
Co-Tx of HIV and HBV	9 (1)	6 (0.3)	35 (4)	
HBV Tx only	44 (5)	119 (7)	102 (12)	
HIV PrEP only	124 (14)	661 (37)	N/A	
HIV PEP only	156 (18)	475 (27)	N/A	
Comorbidities, n (%)				
Hepatitis C virus	40 (5)	57 (3)	66 (8)	<0.0001
Diabetes	46 (5)	98 (6)	115 (13)	
Hypertension	116 (13)	239 (13)	237 (27)	
Chronic kidney disease	19 (2)	31 (2)	59 (7)	
Osteoporosis	2 (0.2)	8 (0.5)	7 (1)	0.2204 ^a
Coronary artery disease	22 (3)	27 (2)	41 (5)	<0.0001
Hyperlipidemia	53 (6)	122 (7)	182 (21)	
Congestive heart failure	11 (1)	21 (1)	24 (3)	0.0059

^aFisher's exact test since 33% of cells have expected counts of <5.

Co-Tx=cotreatment; HBV=hepatitis B virus; N/A=not applicable; PEP=postexposure prophylaxis; PrEP=pre-exposure prophylaxis; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; Tx=treatment.

kidney disease that are more prevalent in Black populations.

Furthermore, this study found that new recipients of TAF were more likely to have comorbidities than new recipients of TDF. Because the extensive literature that implicates TDF use in kidney injury and loss of bone mineral density,^{1,5-7} it is not surprising to see higher prescribing rates of TAF compared with TDF in populations with chronic kidney disease and osteoporosis. However, given that TAF has been shown to worsen lipid levels when compared with TDF,^{17,18} it is notable that TAF is being prescribed more often than TDF in patients with hyperlipidemia and cardiovascular disease.

Interestingly, TAF was more likely to be prescribed in populations with comorbidities compared with TDF

recipients not only after November 2015 (when TAF was approved),⁸ but also compared with TDF recipients before November 2015. Part of why this was seen may be because the health system in this study serves as a referral center so, on average, likely sees more specialized populations than nonreferral centers. Nonetheless, the health system has served as a referral center before and after November 2015. Therefore, this finding suggests that TAF is being prescribed to a broader population than past recipients of TDF to include populations with comorbidities.

TAF may also be prescribed to a larger population because specific combination drug products, such as Biktarvy (bictegravir/FTC/TAF) and Symtuza (darunavir/cobicistat/FTC/TAF),

exist only with TAF and not TDF. Future research should examine prescribing rates of individual TDF and TAF drug products to attribute increases or decreases to specific products.

LIMITATIONS

This study has some limitations to consider. First, TDF and TAF prescribing patterns were examined among those newly started on TDF or TAF between 2014 and 2018 in a single health system. We limited the cohort to new recipients of TDF or TAF between 2014 and 2018 because not all data regarding patient characteristics before 2014 were available; thus, TDF prescribing trends for those who started on TDF before 2014 were not included.

Furthermore, a single health system was examined and whether similar prescribing patterns exist in other health systems is unknown. Nonetheless, the health system includes inpatient and ambulatory care clinics in an academic medical center and 2 large community hospitals, increasing the generalizability of our findings.

Second, comorbidities were classified based on electronic health record-based diagnosis and procedure codes and may have been under- or overreported within the health records. Future studies could use electronic health records and administrative claims data, which may allow for more accurate classification of comorbidities because administrative claims are used for billing.

Third, this study did not examine use of TAF for PrEP because TAF was not approved for PrEP until after our study period. Future studies should examine to what degree TAF versus TDF is being used for PrEP, especially considering recent evidence that, compared with TDF/FTC, TAF/FTC is not cost-effective for PrEP unless there are substantial discounts to its current list price.²² Moreover, a generic version of the combination

TDF/FTC drug product was recently made available,²³ so it will be interesting to see whether there will be an increase in TDF prescribing.

Conclusions

This study examined TDF and TAF prescribing patterns and found that TAF prescribing rates had increased to match TDF prescribing rates approximately 2.5 years after FDA approval. Compared with TDF, TAF was more likely to be newly prescribed to patients with comorbidities, including chronic kidney disease, as well as hyperlipidemia and cardiovascular disease. These results suggest that clinicians are prescribing TAF for a patient population broader than that for TDF to include populations with comorbidities and that prescribers may be prioritizing data in support of an improved kidney safety profile over data suggesting a less favorable effect of TAF on lipids.

DISCLOSURES

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