Real-world impact of switching from tenofovir disoproxil fumarate to tenofovir alafenamide

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Abstract
Although tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) have been evaluated in various clinical trials, limited safety and efficacy data exist in real-world settings. The goal of this retrospective analysis is to assess changes in virological suppression, immunological status, renal function, weight and body mass index (BMI) amongst people living with HIV who switched from a TDF-based to a TAF-based regimen. Of 130 patients included in the final analysis, 53 patients experienced an increase in their viral load upon switching from TDF to TAF therapy whilst 62 patients remained undetectable. For those who experienced a viral blip, 33 (62%) resuppressed by the time of last follow-up, 15 (28%) patients did not have additional labs beyond the last follow-up and concern for failure occurred in 5 (9%) patients. No differences in immunological function, renal function, weight or BMI were observed from before switching to the last follow-up. Although a loss of virological suppression was found upon switching to TAF at subsequent follow-up visits, resuppression ultimately occurred in most patients.

Keywords: antiretroviral, HIV, reverse transcriptase inhibitor, switch, tenofovir.

Introduction
The Centers for Disease Control and Prevention estimated that 1.2 million Americans and 38 million people worldwide were living with human immunodeficiency virus (HIV) by the end of 2018.¹ Treatment of HIV has undergone substantial improvements primarily due to an increase in the effectiveness and a decrease in adverse effects associated with antiretroviral (ARV) therapy. These improvements have led to decreased morbidity and mortality and reductions in viral transmission.²

Tenofovir disoproxil fumarate (TDF) is a nucleoside reverse transcriptase inhibitor (NRTI) and the first approved oral prodrug of tenofovir (TFV) used in the treatment of HIV since 2001. It is part of the preferred NRTI backbone and a component of more than half of the regimens recommended by the United States Department of Health and Human Services.² Whilst TDF is generally well tolerated, there are reports of reduced bone mineral density (BMD), nephrotoxicity and Fanconi syndrome, which is characterized as an impairment in the proximal renal tubules leading to excessive loss of substances in the urine causing metabolic acidosis, nephrotoxicity or fractures.²

Tenofovir alafenamide (TAF), the newer prodrug of TFV, has greater stability in plasma and allows for the active metabolite to achieve 5–7-fold higher concentrations in peripheral blood mononuclear cells with 91% lower plasma TFV levels. These lower TAF plasma trough concentrations result in less nephrotoxicity and declines in BMD compared to TDF whilst maintaining efficacy.³–¹¹ Despite these advantages, TAF increased lipid levels compared to TDF and postmarketing studies have demonstrated that weight and body mass index (BMI) increase with TAF compared to TDF.¹²

Since the initial FDA approval of TAF in 2015,¹³ it has been widely accepted that TAF is superior to TDF based on safety and efficacy, resulting in a clinical shift toward the use of TAF.¹⁴ Whilst there is strong evidence from clinical trials, real-world data vary. Therefore, this study aimed to assess changes in virological suppression, immunological status, renal function...
and weight/BMI amongst people living with HIV who switched from a TDF-based to a TAF-based regimen at the University of Illinois at Chicago Hospital and Health Sciences System Community Clinic Network (UCCN), where TAF was quickly adopted as the preferred NRTI to treat HIV.

**Methods**

This single-centre, multiclinic retrospective cohort study was conducted using electronic medical records of people living with HIV who switched from a TDF-based to a TAF-based regimen at UCCN from January 2016 to March 2019. Medical records were reviewed at the visit prior to the switch and every 3–4 months after the switch as part of standard care up to a maximum of four follow-up visits or approximately 12 months using a standardized REDCap (Version 9.1.0, May 31, 2019, Vanderbilt University, Nashville, TN, USA) data entry tool. Adult patients at least 18 years of age receiving care from UCCN, diagnosed with HIV1, on a TDF-based ARV regimen for greater than 6 months before switching to a TAF-based regimen without changing any other ARV component, and with at least one set of labs including HIV1 RNA before and after the switch were included. Prisoners and patients receiving TDF for pre-exposure prophylaxis or hepatitis B virus mono-infection were excluded. The study was approved by the Office for the Protection of Research Subjects Institutional Review Board with a waiver of consent granted.

The primary outcome of interest was the HIV1 RNA viral load (VL) before and after switching. Patients were considered virologically suppressed if HIV1 RNA was ≤50 copies/mL. A detectable VL was defined as an HIV1 RNA of >50 copies/mL. Viral blip was defined as an isolated VL of 51–199 copies/mL after virological suppression that was followed by a return to virological suppression.15 Concern for failure (CFF) was defined as VL >200 copies/mL after being <200 copies/mL, based on the Department of Health and Human Services definition of virological rebound.2 HIV1 RNA was quantified by the COBASr AmpliPrep/COBASr TaqManr HIV-1 Test, Version 2.0.16 The quantifiable range of the assay is 20–10,000,000 copies of HIV1 RNA per millilitre of plasma. Secondary outcomes were changes indicated by CD4 count (cells/mm³).

Continuous variables were compared using paired Student’s t-tests if parametric and Mann–Whitney U tests if non-parametric. Categorical variables were evaluated via χ², Fisher’s exact or McNemar’s test as appropriate. A two-tailed significance of ≤0.05 was considered statistically significant. All analyses were performed using SPSS® Version 26 (IBM Corporation, Armonk, NY, USA).

**Results**

Of 202 patients evaluated, 130 were included in the final analysis; 72 patients were excluded from the study due to lack of available data. The majority of patients had normal renal function (91%) (serum creatinine (Scr) <1.3 mg/dL) and overweight (BMI ≥25–29.9 kg/m²) or obesity (BMI ≥30 kg/m²) (63%) (Table 1). The mean ±SD age was 47±11 years. At the time of switching, 31% of the study population had an acquired immunodeficiency syndrome (AIDS) diagnosis. The median duration of TDF therapy before the switch was 71 (range 2–197) months.

Amongst the 130 patients who were switched from TDF to TAF, the majority were virologically suppressed before switching (Table 2). Of the 15 patients who had a VL of >50 copies/mL before switching, 11 (73%) achieved virological suppression based on the last known lab. Baseline viraemia was most common with integrase strand transfer inhibitors and multiclass regimens (33% for each). For patients virologically suppressed at baseline, they were significantly more likely to remain undetectable at the last follow-up visit after switching (p=0.031) (Table 2). Before switching, 11.5% of patients had CFF on TDF-based regimens but, after an average duration of 1 year on TAF-based regimens, <1% of patients had CFF. In the 53 patients who experienced an increase in their VL, no differences in viral blip frequency or virological failure postblip were observed after TAF switching. Of the 53 patients who experienced a viral blip after switching, 33 (62%) resuppressed by the time of the last follow-up, 15 (28%) patients did not have additional labs beyond their last follow-up on record and CFF occurred in 5 (9%) patients. Additionally, based on the last available follow-up, 62 patients who switched from TDF to TAF maintained virological suppression.

At the time of switching from a TDF-based to a TAF-based regimen, the mean (SD) weight was 82.8 kg (20.4), with 34% (n=45) classified as normal weight, 34% (n=44) overweight, 29% (n=38) obesity and 2% (n=3) underweight (Table 1) according to the WHO BMI classification of weight status.17 There were no statistically significant differences after switching from a TDF-based to a TAF-based regimen in any of the secondary outcomes (Table 3). The average (SD) baseline BMI whilst on TDF therapy was 27.7 (6.2) and after approximately 1 year on TAF therapy it was 28.2 (6.2; p=0.1768). The mean (SD) Scr was 0.99 mg/dL (0.24) and 1.01 mg/dL (0.23) before and after switching, respectively (p=0.5668). The median baseline CD4 count was 606 cells/mm³ (295) and 626 cells/mm³ (316) before and after switching, respectively (p=0.6413).

**Discussion**

We observed an overall maintenance in virological suppression at the time of the last follow-up in our cohort of patients switched from a TDF-based to a TAF-based regimen without changing any other ARV regimen components, even in patients who experienced viral blips after switching. The initial observation of a viral blip may be due to transitioning between TDF-based and TAF-based ARV therapy, where
Table 1. Baseline characteristics (n=130).

| Characteristic                                    | Value         |
|---------------------------------------------------|---------------|
| Age (years), mean (±SD)                           | 47 (±11)      |
| Male sex, n (%)                                   | 100 (77)      |
| Race or ethnicity, n (%)                          |               |
| Black                                             | 64 (49)       |
| Hispanic                                          | 37 (29)       |
| White                                             | 22 (17)       |
| Other or not specified                            | 7 (5)         |
| AIDS diagnosis (yes), n (%)                       | 40 (31)       |
| ART anchor drug before switching, n (%)           |               |
| NNRTI                                             | 45 (35)       |
| INSTI                                             | 42 (32)       |
| PI                                                | 29 (22)       |
| Multiclass                                        | 14 (11)       |
| Length of TDF before switching (months, n=125), median (range) | 71 (2–197) |
| SCr <1.3 mg/dL (n=128) (%)                        | 117 (91)      |
| Weight (kg), mean (±SD)                           | 82.84 (20.41) |
| BMI classification (kg/m²), n (%)                 |               |
| Underweight (<18.5)                               | 3 (2)         |
| Normal weight (18.5–25)                           | 45 (35)       |
| Overweight (25–30)                                | 44 (34)       |
| Obesity (>30)                                     | 38 (29)       |

AIDS, autoimmune deficiency syndrome; ART, antiretroviral therapy; BMI, body mass index; INSTI, integrase strand transfer inhibitor; NNRTI, nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; SCr, serum creatinine; TDF, tenofovir disoproxil fumarate.

Table 2. Change in HIV viral load before and after switching from TDF to TAF.

|                  | Virological suppression (<50 copies/mL), n (%) | Detectable viral load (≥50 copies/mL), n (%) |
|------------------|-----------------------------------------------|---------------------------------------------|
| Before switching (n=130) | 115 (88.5)                                     | 15 (11.5)                                   |
| After switching   |                                               |                                             |
| Follow-up 1 (n=130)  | 111 (85.4)                                     | 19 (14.6)                                   |
| Follow-up 2 (n=120)  | 91 (75.8)                                      | 29 (24.2)                                   |
| Follow-up 3 (n=105)  | 90 (85.7)                                      | 15 (14.3)                                   |
| Follow-up 4 (n=93)   | 84 (90.3)                                      | 9 (9.7)                                     |

HIV, human immunodeficiency syndrome; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 3. Change in secondary outcomes before and after switching from TDF to TAF.

| Mean (±SD)               | Baseline | Last follow-up | p value |
|--------------------------|----------|----------------|---------|
| CD4 count, cell/mm³      | 606 (295) | 626 (316)      | 0.6413  |
| Serum creatinine, mg/dL  | 0.9875 (0.2385) | 1.0058 (0.2281) | 0.5668  |
| Weight, kg               | 82.84 (20.41) | 83.55 (18.59)  | 0.4454  |
| BMI, kg/m²               | 27.70 (6.23)  | 28.24 (6.23)   | 0.1768  |

BMI, body mass index; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
TAF-based therapy was associated with a lower systemic exposure of tenofovir compared to TDF. The majority of patients in our analysis had longstanding HIV infection as evidenced by the median time on TDF therapy, which was controlled by ARV therapy at the time of switching. Given these characteristics and strong clinical trial evidence supporting the non-inferiority efficacy of TAF to TDF, it would seem unlikely that substituting TFV prodrug formulations would result in the loss of virological suppression. However, in clinical practice, a sudden rise in VL following the initiation of a new regimen can be alarming to both clinicians and patients. Results of our study provide reassurance that experiencing an initial increase in VL after switching from a TDF-based to a TAF-based regimen does not place patients at an increased risk for additional viral blips or virological failure as the majority of patients in our cohort resuppressed by the time of the last follow-up.

Patients in our cohort who were virologically suppressed on TDF at the time of switching were more likely to be virologically suppressed on TAF at the time of the last follow-up. However, the results of our study also support switching from TDF to TAF, whilst maintaining other ARVs, in patients not virologically suppressed on their TDF-based regimen. The majority of patients in our cohort with an HIV VL of >50 copies/mL at the time of switching achieved virological suppression at the time of the last follow-up after switching to TAF. This included patients with CFV before switching, in which receiving add-on therapy with integrase strand transfer inhibitors or with multidrug resistance was most common. After approximately 1 year, switching from a TDF-based to a TAF-based regimen significantly reduced CFV in our cohort. Thus, our results do not support waiting for virological (re)suppression before switching tenofovir formulations. As with all ARV switches, individual risks and benefits must be considered using a patient-centred approach. Regarding tenofovir, this often involves discussion of long-term adverse effects, including renal and bone toxicities.

Many studies have documented the renal-sparing properties of TAF therapy in patients with declining renal function at baseline compared to TDF. The majority of patients analysed in our cohort had normal baseline renal function on TDF, which was not significantly affected after switching to TAF. These results match previously reported TAF data. However, early randomized clinical trials and postmarketing reports failed to find an association between TDF and renal toxicity and the development of Fanconi syndrome. This was in contrast to other supporting data that demonstrated tenofovir caused significant toxicity in proximal tubular cells. The conflicting results between clinical trials and case reports may be explained by the strict inclusion and exclusion criteria of clinical trials. A pooled analysis of 26 clinical trials compared renal adverse events between participants taking TAF-based regimens versus those taking TDF-based regimens. This study determined that fewer individuals on TAF compared to TDF discontinued due to a renal adverse event and there were no cases of proximal renal tubulopathy in participants receiving TAF-based regimens.

Notwithstanding the limited sample size, our findings support the use of TAF in patients with overweight and obesity. At the time of switching to a TAF-based regimen, most patients were considered at or above a normal BMI and had no significant change in weight or BMI after switching. A study explored factors promoting weight gain in eight industry-sponsored studies. This study found that weight gain was greater with recently approved ARV therapy as well as a low CD4 count, high VL, female sex and Black race. Female sex, an age under 50 years, and individuals with obesity at baseline experienced lower but statistically significant increases in weight. These results mirror our findings because a mean 0.99 kg greater weight gain was noted in Black participants. Nonetheless, this study also highlights that weight gain is universal in clinical studies after initiating ARV therapy based on demographic and HIV-related factors along with the type of ARV therapy used in the management of HIV.

Our study is not without limitations. As this was an observational study, we were unable to prove causal relationships between TAF and the outcomes of interest. We attempted to control for confounding variables based on eligibility criteria and analysis of the data. As an example, we were unable to collect data on potential drug interactions and medication adherence, which can account for viral blips or loss of virological suppression. Additionally, our study did not assess changes to BMD or lipids, which are notable concerns with tenofovir. Even when recommended, dual-energy X-ray absorptiometry scanning is not always conducted in practice due to limited resources. Although our clinic network consisted of multiple HIV clinics located throughout Chicago, we are a single academic medical centre; therefore, combining this fact with our small sample size and a decline in available results over the study period, the findings from our study may not be entirely generalizable to other clinical populations. In context with other available data, our results help inform the real-world implications of patients switching from a TDF-based to a TAF-based regimen.

**Conclusion**

In this study, switching from a TDF-based to a TAF-based regimen revealed no significant differences in renal function, weight or BMI, or immunological status. Although, a loss of virological suppression was observed upon switching to TAF, at subsequent follow-up visits resuppression occurred in most patients. This study highlights that, if the development of post-TAF viral blips occurs, virological resuppression is possible with continued adherence in a real-world clinical population.
Contributions: MEB, RMB, TDC, SMM, ROS and EW conceived the presented idea and designed the study. EW conducted preliminary data analyses. MJ conducted an additional data analysis under the guidance of MEB, and SMM, MEB, MJ and SMM wrote the manuscript. All authors discussed the results and approved the final manuscript prior to submission. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: TDC obtained employment at Gilead Sciences, Inc. as a medical scientist in May 2020. RMB, SMM and ROS are investigators in a Merck-sponsored study. RMB, MJ and SMM are investigators in a Moderna-sponsored study. RMB is an investigator in a Janssen-sponsored study. EW serves on the speaker’s bureau for Melinta Therapeutics, Astellas Pharma and Allergan Plc. and on the advisory board for GenMark Diagnostics and Shionogi. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2021/06/dic.2021-2-1-COI.pdf

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