

Alopecia After Switch to Tenofovir Alafenamide in 6 African American Women

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No cases of tenofovir alafenamide (TAF)-induced alopecia have been reported in the literature. We describe 6 cases of hair loss in African American female patients after switching to TAF and aim to raise awareness about this potential adverse effect of TAF, which could predominate in certain patient populations.

Keywords. alopecia; HIV; tenofovir alafenamide.

Tenofovir disoproxil fumarate (TDF) was first approved by the US Food and Drug Administration (FDA) in 2001 for the treatment of HIV and was included in most guidelines for the initial treatment of HIV-infected patients [1]. Despite being potent and well tolerated, it was associated with significant renal and bone toxicities [1]. In 2015, a novel tenofovir prodrug, tenofovir alafenamide (TAF), was approved as a combination therapy for the treatment of HIV. TAF had fewer renal and bone adverse effects, making it a more desired nucleotide reverse transcriptase backbone component.

Alopecia is a rare but reported side effect of some protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nucleos(t)ide reverse transcriptase inhibitors (NRTIs) [2]. Headaches, nausea, and diarrhea remain among the most common reported side effects of TAF-containing regimens [1]; however, no reports of alopecia and hair thinning have been reported in the literature with the use of TAF. This case series represents, to the best of our knowledge, the first report of alopecia and hair thinning associated with TAF therapy in African American (AA) females.

CASES

This is a case series reported from an academic outpatient HIV practice located in Detroit, Michigan. Among the 2139 patients

who followed up at this clinic in 2018, 579 were AA females (27%). Six HIV-infected AA females developed alopecia after switching from TDF- to TAF-containing regimens (Table 1). All patients who tolerated TDF were switched to TAF because of its better long-term safety profile. Their age ranged between 40 and 61 years. Hair loss was focal and involved the scalp in all patients (Figure 1A–D). One patient had patchy hair loss involving the back of the head (Figure 1A). Time-to-onset of alopecia after switching to TAF ranged between 2 months and 1 year; however, 4 out of 6 patients reported hair loss after 2–4 months. No pain, pruritus, or tenderness was reported by any of the patients, and there was no evidence of scarring, flaking, or inflammation on physical examination. All patients had sustained viral suppression at the time of evaluation, their CD4 T-lymphocyte (CD4) count (range) was persistently above 500 (600–1312) cells/ μ L, and they had no clinical evidence of active infections. No metabolic derangements that would explain the alopecia were identified on basic metabolic panels, liver function tests, albumin, total protein, or thyroid-stimulating hormone levels. A complete blood count ruled out severe anemia as the cause of alopecia in all patients. A sexually transmitted disease (STD) workup including syphilis, chlamydia, and gonorrhea DNA amplification testing, hepatitis B surface antigen, hepatitis C antibodies, and a treponemal enzyme immunoassay was nonrevealing. No new medications other than TAF were introduced at the time of development of alopecia, and other medications that were already being taken by the patients were not known to be associated with alopecia. A detailed history and physical examination ruled out psychological distress, severe caloric restrictions, or changes in lifestyle habits (such as use of new shampoos and hair products) as the cause of hair loss. One patient started braiding her hair following the alopecia, and another patient had been performing tight hair braiding for many years (Figure 1B and C); however, both reported alopecia only after switching to TAF. In an attempt to reverse the alopecia, 5 patients were switched to abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) and DTG/rilpivirine (RPV), respectively (Table 1). Two out of the 5 patients followed up in clinics and had some objective hair regrowth in all areas of hair loss, whereas the remaining 3 were contacted over the phone and reported subjective, noticeable improvement. Hair regrowth was noticeable within 1–5 months after discontinuation of TAF. One patient elected to try conservative measures for hair regrowth before switching antiretroviral therapy (ART) but had no noticeable hair regrowth upon further follow-up at 6 and 12 months.

DISCUSSION

Hair follicles go through phases of active growth (anagen), involution (catagen), and rest (telogen) before finally shedding

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Table 1. Patient Characteristics

Patient	Age, y; Gender; Ethnicity	ARVs Before Onset of Alopecia	ARVs at Onset of Alopecia	Other Medications	Time to Onset	HIV Viral Load, copies/mL	CD4 T-lymphocyte Count, cells/ μ L	Syphilis EIA	Management	Outcome
1	45; F; AA	FTC/ATV/RTV/TDF	FTC/DTG/TAF	Cetirizine	7 mo	67	1056	Negative	Switched to ABC/DTG/3TC	Improvement 4–5 mo after switch
2	44; F; AA	FTC/RPV/TDF	FTC/RPV/TAF	Lisinopril Hydrochlorothiazide Amlodipine	1 y	Undetectable	700	Negative	Switched to DTG/RPV	Improvement 2–3 mo after switch
3	40; F; AA	FTC/RPV/TDF	FTC/RPV/TAF	Bupropion (discontinued 1 y before switching to TAF)	3 mo	Undetectable	600	Negative	Observation	No improvement
4	49; F; AA	FTC/RPV/TDF	FTC/RPV/TAF	Albuterol sulfate Fluticasone/salmeterol Atorvastatin Acetaminophen Zyrtec	3 mo	Undetectable	1312	Negative	Switched to DTG/RPV	Improvement 2–3 mo after switch
5	42; F; AA	FTC/RPV/TDF	FTC/RPV/TAF	Cholecalciferol Ergocalciferol	2 mo	Undetectable	1043	Negative	Switched to DTG/RPV	Improvement 1 mo after switch
6	61; F; AA	FTC/EFV/TDF	FTC/BIC/TAF	Ergocalciferol Metformin Chlorthalidone Atorvastatin	4 mo	Undetectable	806	Negative	Switched to DTG/RPV	Improvement 1–2 mo after switch

Abbreviations: 3TC, lamivudine; AA, African American; ABC, abacavir; ARVs, antiretrovirals; ATV, atazanavir; BIC, bictegravir; DTG, dolutegravir; EFV, efavirenz; F, female; FTC, emtricitabine; RPV, rilpivirine; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

(exogen) [3]. Most hair follicles in a normal scalp are in the anagen phase, whereas only 5%–10% are in the telogen phase, with an average of 50–150 hairs shed daily [3]. The mechanism of drug-induced alopecia often involves the disruption of the hair cycle either during the anagen phase (anagen effluvium) or telogen phase (telogen effluvium). Cytotoxic drugs and radiation therapy commonly affect rapidly proliferating cells including hair follicles in the anagen phase. Anagen effluvium usually occurs 1–4 weeks after initiation of the offending agent and is characterized by diffuse hair loss, which can involve all body sites [2, 4]. Telogen effluvium, on the other hand, occurs when follicles in the anagen phase are precipitated prematurely into the telogen phase, leading to hair loss 2–3 months after the insult [3]. Alopecia in HIV-infected patients is multifactorial and may be attributed to advanced AIDS, opportunistic infections, STDs, metabolic and nutritional derangements, and medication side effects, all of which are thought to induce alopecia most commonly through telogen effluvium [2, 3, 5]. Therefore, in a patient with ART-induced alopecia, we often expect to see diffuse, nonscarring hair loss occurring 2–3 months after initiation of therapy, with improvement of hair loss 3–6 months after discontinuation of the offending drug [3]. Cosmetically significant growth may take up to 12–18 months [3].

In a review article by Woods et al. including 46 patients with ART-induced alopecia, the most commonly implicated drugs were protease inhibitors (PIs), followed by NRTIs [2]. Among PIs, indinavir (IDV) followed by lopinavir (LPV) and ritonavir (RTV) were the most common drugs associated with alopecia. Among NRTIs, hair loss was most frequently suspected with 3TC therapy, whereas FTC, ABC, and zidovudine (ZDV) were reported in a few isolated cases [2, 5]. To the best of our knowledge, no cases of TAF-induced alopecia have been reported in the literature so far.

The mechanism of NRTI-induced alopecia is not well described; however, NRTIs inhibit the mitochondrial polymerase γ , leading to inhibition of mitochondrial DNA replication, thereby inducing premature aging phenotypes including alopecia in mouse models [5]. Hair concentrations of tenofovir strongly correlate with concentrations of tenofovir diphosphate in dried blood samples [6]. Moreover, tenofovir concentration measurements in hair reflect cumulative exposure to the drug; this has been suggested as a method for therapeutic drug monitoring [7]. It is unclear whether tenofovir accumulation in the hair contributes to the alopecia seen with TAF. A recent unpublished study presented by Okochi et al. at the AIDS Conference in 2018 concluded that tenofovir concentrations in hair samples for TAF and TDF were comparable [8]. This conclusion suggests that hair drug concentrations of tenofovir might not be contributing to hair loss as, to the best of our knowledge, no cases of TDF-induced alopecia have been reported in the literature.

The onset of hair loss in most published reports occurred an average of 2–6 months after initiation of ART; however, some



Figure 1. A, Patchy alopecia involving the back of the head of a patient 7 months after initiation of tenofovir alafenamide (TAF) suggestive of alopecia areata. B, C, Focal hair loss with no scaling or scarring involving the scalp of patients practicing tight hair braiding 2 months and 3 months after initiation of TAF, respectively. D, Focal hair thinning involving the frontal scalp of a patient 4 months after initiation of TAF.

cases of alopecia after 1–2 years of therapy have also been reported [2]. Complete hair loss involving multiple sites of the body, hair thinning, hair loss in clumps, and patchy hair loss were the most commonly used descriptive terms. Treatment often included the discontinuation of the offending medication. In most patients, hair regrowth occurred within months after switching to another ART regimen [2]. Five out of 6 patients in this series had an onset of alopecia 2–7 months after initiation of TAF, whereas 1 reported hair thinning around 1 year after therapy. Hair loss was focal and involved the scalp in all cases. One patient had patchy hair loss suggestive of alopecia areata (Figure 1A). Other causes of alopecia such as advanced AIDS, sexually transmitted infections including syphilis, severe anemia, psychological distress, and caloric restrictions were ruled out.

The temporal sequence of hair loss after initiation of TAF in our subjects and the improvement of alopecia in 5 of the patients 1–5 months after discontinuation of TAF suggest a cause–effect relationship. There are no previous reports of TAF-induced alopecia; however, the timeline and patterns of hair loss are consistent with previously published reports of ART-induced alopecia. Based on the Naranjo Adverse Drug Reaction Probability Scale [9], our patients have a score of +3, indicating a possible causality between TAF and alopecia.

In this series, the 6 cases of alopecia occurred in AA women. AAs account for half of all HIV diagnoses in the United States while representing only 12% of the population [10]. AA women account for 60% of HIV diagnoses among all women [10], and despite being disproportionately affected, they are poorly represented in clinical trials. The demographic data presented in clinical trials are not stratified in a way that would allow for the extrapolation of the numbers and percentages of recruited AA females; however, a low percentage of recruitment can be deduced. For example, the percentage of AAs recruited in TAF trials ranges between 11% and 30%, whereas the percentage of recruitment of female patients in general ranges between 4% and 15%, suggesting that the participation of AA females is low [1, 11, 12]. Diversity of subjects in clinical trials is crucial to assessing the safety and efficacy of new treatments across a broad population and to ensuring generalizability of findings. Therefore, some of the side effects of TAF might be

underreported among AA women. Hair loss is more likely to affect the quality of life and healthy social functioning of women as compared with men, as hair is often a social reflection of a women’s femininity and attractiveness [3, 13]; therefore, it is important that health care providers be aware of alopecia as a potentially distressing side effect of TAF.

This case series is, to the best of our knowledge, the first to describe alopecia as a potential adverse side effect of TAF; however, it carries some limitations. A hair-pull test was not performed on any of the patients. This test is typically performed by applying a gentle upward pull on a small portion of a patient’s hair at different locations of the scalp. A positive pull test (2 or more hairs removed) would have been an objective finding supporting excessive hair shedding, which could be seen in telogen or anagen effluvium, alopecia areata, and other conditions depending on the areas of the scalp that are affected [14]. Hair samples were not sent for microscopy, and no scalp biopsies were performed. Also, hair loss in HIV patients can be multifactorial, and exclusion of all alternative causes of hair loss while proving a definite adverse drug reaction is often not feasible without a well-designed clinical study.

CONCLUSIONS

TAF is an appealing alternative to TDF as an NRTI backbone for the treatment of HIV. This report aims to raise awareness among health care practitioners about alopecia as a potentially distressing adverse effect of TAF that could predominate in certain underrepresented patient populations. Increased representation of AA women in HIV/AIDS clinical trials is important to identifying issues that may be unique to some populations.

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