Case Report: Reversal of Integrase Inhibitor– and Tenofovir Alafenamide–Related Weight Gain After Switching Back to Efavirenz/Emtricitabine/ Tenofovir DF

F. Will Pohlman,1 Kara S. McGee,2,3 and Mehri S. McKellar2
1Duke University School of Medicine, Durham, North Carolina, USA, 2Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina, USA, and 3Duke University School of Nursing, Durham, North Carolina, USA

We report a case of substantial weight gain in a virologically suppressed patient with HIV after changing his antiretroviral therapy from efavirenz/emtricitabine/tenofovir DF to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide with subsequent rapid weight loss upon switching back. The role of antiretrovirals in weight gain and loss and patient- and HIV-specific factors are discussed.

Keywords. HIV; integrase; tenofovir alafenamide; weight gain.

CASE REPORT

A 33-year-old African American male who was virologically suppressed on antiretrovirals (ARVs) presented to the clinic complaining of significant weight gain. At the time of HIV diagnosis 8 years prior (November 2012), his initial HIV-1 RNA viral load was 8300 copies/mL with a baseline CD4 count of 590 cells/mm3. The patient had no other significant medical history except for mild tinea versicolor, treated with 2 short courses of fluconazole. One month after HIV diagnosis (December 2012), the patient was started on efavirenz/emtricitabine/tenofovir DF to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide with subsequent rapid weight loss upon switching back. The role of antiretrovirals in weight gain and loss and patient- and HIV-specific factors are discussed.

To our knowledge, this is the first reported case of significant weight reversal of antiretroviral therapy (ART) switch–induced weight gain upon switching back to the original regimen. Switching ART is associated with more weight gain than maintaining regimens, and the degree of weight gain may be influenced by both baseline and postswitch agents [1]. Therefore, our patient's weight changes may be due to weight suppressive effects of EFV/FTC/TDF, weight gain effects of EVG/COBI/FTC/TAF, withdrawing weight suppressive/gain effects, or some combination.

Weight loss or suppressed weight gain associated with TDF use has been noted in several patient populations. In the iPrEx trial of TDF/FTC as pre-exposure prophylaxis, seronegative patients receiving TDF/FTC gained less weight, on average, than those receiving placebo and were significantly more likely to experience unintentional weight loss of ≥5% [2]. In the DISCOVER trial, which compared TDF with TAF in pre-exposure prophylaxis regimens, participants in the TDF arm lost weight in the first 24 weeks and returned to their baseline weight by week 48, similar to our patient's initial weight loss and then return toward baseline [3]. Among people with HIV (PWH), patients in the GEMINI trials receiving dolutegravir (DTG)+TDF/FTC gained less weight than those receiving DTG+lamivudine (3TC; 3.7 kg vs 2.4 kg by week 144) [4]. This weight loss or weight gain suppression with ART may be an off-target effect, and perhaps not entirely healthy. In the IMPAACT 2010/VESTED trial of ART initiation in pregnant women, patients receiving EFV/FTC/TDF gained less weight than those

DISCUSSION

© The Author(s) 2021. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Received 29 June 2021; editorial decision 15 July 2021; accepted 26 July 2021.
Correspondence: Mehri McKellar, Duke University Medical Center, Durham, NC 27710 (mehri.mckellar@duke.edu).
receiving DTG/FTC/TAF or DTG/FTC/TDF, were furthest from the Institute of Medicine–recommended weekly weight gain in the second and third trimesters, and had more adverse pregnancy outcomes [5].

Integrase strand transfer inhibitor (INSTI)–associated weight gain has been reported in a growing number of recent studies among both treatment-naive and treatment-experienced patients [6–9]. An analysis of 8 randomized controlled clinical trials of ART-naive PWH found that INSTI-containing regimens were associated with more weight gain than NNRTI- and PI-based ART regimens [10]. This appears to be a class effect, although bictegravir (BIC) and DTG were associated with more weight gain than cobicistat-boosted EVG (BIC, 4.24 kg; DTG, 4.07 kg; and EVG/COBI, 2.72 kg) over 96 weeks [10]. Significant weight gain among virologically suppressed PWH after switching from EFV/FTC/TDF to an INSTI-based regimen, similar to our patient, has also been reported [11]. Weight change with INSTI therapy appears to be heterogeneous, however. While the average weight gain with INSTI use is moderate, some patients, such as our patient, experience substantial weight gain (>10% increase in bodyweight) [10, 12].

TAF has also been implicated as a potential cause of weight gain in several patient populations. In the DISCOVER trial, participants in the TAF arm had a mean body weight increase of 1.1 kg at week 48 compared with the initial weight loss and return to baseline in the TDF group [3]. Among virologically suppressed PWH, switching from TDF- to TAF-containing ART regimens, with or without changing other regimen components, is significantly associated with pronounced weight gain, which can lead to concerning metabolic complications including elevated serum lipid levels [13–15]. In the ADVANCE trial, the TAF arm was associated with treatment-emergent obesity, particularly among women [16]. TAF was significantly associated with substantial weight gain compared with all other NRTIs in trials among those initiating ART [10]. TAF appears to be associated with weight gain in HIV-negative, treatment-naive, and virologically suppressed patients and may have contributed to the pronounced weight gain of our patient.

The mechanisms underlying specific susceptibility to ARV-associated weight changes are currently unknown. Patient- and HIV-specific factors may influence weight response, with substantial weight gain being more likely among female and Black patients as well as those with lower baseline BMI, lower CD4 cell counts, and higher HIV-1 RNA copies [10, 17]. This heterogeneous response may explain the lack of significant change in weight gain with INSTI therapy reported by some studies due to
variations in demographics and HIV-specific factors among included participants [18, 19]. There is growing research regarding pharmacogenetics predicting weight gain or loss with specific ARVs. In a retrospective investigation, patients with CYP2B6 polymorphisms (slow metabolizers of EFV) gained more weight following a switch from an EFV- to INSTI-based regimen, potentially reflecting withdrawal of the inhibitory effect of higher EFV concentrations on weight gain [20]. Conversely, patients with CYP2B6 genotypes associated with extensive metabolism of EFV experienced similar weight gain with EFV-based ART as patients with an INSTI-based regimen [21]. The CYP2B6 alleles associated with impaired metabolism of EFV are more common among individuals of African ancestry, such as our patient, potentially contributing to observed differences in weight gain by race [22]. Further identification and understanding of patient- and HIV-specific factors associated with weight gain, particularly substantial weight gain, may influence treatment decisions.

CONCLUSIONS

We report a case of substantial weight gain (28% increase from baseline) in a virologically suppressed young African American male with HIV after switching his ART regimen from EFV/FTC/TDF to ETV/COBI/FTC/TAF. Remarkably, the patient quickly lost a significant portion of the weight gained within 6 months when switched back to his original regimen. Both INSTIs and TAF are associated with substantial weight gain, while TDF (especially with EFV) is associated with weight loss or weight gain suppression, with observed differences in susceptibility by patient- and HIV-specific factors. Understanding these factors may aid in predicting substantial weight gain to guide management for PWH.

Acknowledgments

Financial support. None.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. Patient consent was obtained. This conforms with standards of the Duke Health Institutional Review Board for publishing case reports.

Author contributions. K.S.M. and M.S.M. contributed to clinical management. All authors coordinated the case report, collected clinical and laboratory data, discussed the results, and wrote and approved the manuscript.

References

1. Erlandson KM, Carter CC, Melbourne K, et al. Weight change following antiretroviral therapy switch in people with viral suppression: pooled data from randomized clinical trials. Clin Infect Dis. 2021; ciab444.

2. Grant RM, Lama JR, Anderson PL, et al; iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010; 363:2587–99.

3. Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV preexposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet 2020; 396:239–54.

4. Cahn P, Madero JS, Arribas JR, et al. Durable efficacy of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral treatment-naive adults with HIV-1 infection—3-year results from the Gemini studies. J Acquir Immune Defic Syndr 2020; 83:310–8.

5. Lockman S, Brummel SS, Ziemba L, et al; IMPACTA 2010/VESTED Study Team and Investigators. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPACTA 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet 2021; 397:1276–92.

6. Wu KS, Anderson C, Little SJ. Integrase strand transfer inhibitors play the main role in greater weight gain among men with acute and early HIV infection. Open Forum Infect Dis 2021; 8:XXX–XX.

7. Bourn J, Rebeiro PJ, Turner M, et al. Greater weight gain in treatment-naive persons starting dolutegravir-based antiretroviral therapy. Clin Infect Dis 2020; 70:1267–74.

8. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. Curr Opin Infect Dis 2020; 33:10–9.

9. Bakal DR, Coelho LE, Luz PM, et al. Obesity following ART initiation is common and influenced by both traditional and HIV ART-specific risk factors. J Antimicrob Chemother 2018; 73:217–85.

10. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. Clin Infect Dis 2020; 71:1379–89.

11. Norwood J, Turner M, Bolill C, et al; Brief report: weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. J Acquir Immune Defic Syndr 2017; 76:257–31.

12. Verhoeft SO, Boyd A, Wit FW, et al; AGEuHIV Cohort Study Group. Generally rare but occasionally severe weight gain after switching to an integrase inhibitor in virally suppressed AGEuHIV cohort participants. PLoS One 2021; 16:e0251205.

13. Schafer JJ, Sassa KN, O’Connor JR, Shimada A, Keith SW, DeSimone JA. Changes in body mass index and atherosclerotic disease risk score after switching from tenofovir disoproxil fumarate to tenofovir alafenamide. Open Forum Infect Dis 2019; 6:ofz414.

14. Mallon PW, Brunet L, Hsu RK, et al. Weight gain before and after switch from TDF to TAF in a U.S. cohort study. J Int AIDS Soc 2021; 24:e25702.

15. Surial B, Mugglin C, Calmy A, et al; Swiss HIV Cohort Study. Weight and metabolic changes after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in people living with HIV: a cohort study. Ann Intern Med 2021; 174:758–67.

16. Venter WDF, Moorhouse M, Sokhela S, et al; Dolutegravir plus two different protease inhibitors plus lamivudine (3TC) in antiretroviral treatment–naive adults with HIV-1 infection—an 8-week study. Clin Infect Dis 2020; 70:1267–74.

17. Bedimo R, Adams-Huet B, Taylor BS, Lake J, Luque A. 538. Integrase inhibitor-based HAART is associated with greater BMI gains in Blacks, Hispanics, and women. Open Forum Infect Dis 2018; 5(Suppl 1):S199.

18. Burns JE, Stirrup OT, Dunn D, et al; AGEhIV Cohort Study Group. Generally rare but occasionally severe weight gain after switching to an integrase inhibitor in virally suppressed adults with HIV. AIDS 2020; 34:109–14.

19. Tiraoboshi J, Navarro-Alcaraz A, Giralt D, et al. Changes in body fat distribution and metabolic changes after switching from tenofovir disoproxil fumarate to tenofovir alafenamide. Open Forum Infect Dis 2019; 6:ofz414.

20. Cahn P, Madero JS, Arribas JR, et al. Durable efficacy of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral treatment-naive adults with HIV-1 infection—3-year results from the Gemini studies. J Acquir Immune Defic Syndr 2020; 83:310–8.

21. Lockman S, Brummel SS, Ziemba L, et al; IMPACTA 2010/VESTED Study Team and Investigators. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPACTA 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet 2021; 397:1276–92.

22. Wu KS, Anderson C, Little SJ. Integrase strand transfer inhibitors play the main role in greater weight gain among men with acute and early HIV infection. Open Forum Infect Dis 2021; 8:XXX–XX.

23. Bourn J, Rebeiro PJ, Turner M, et al. Greater weight gain in treatment-naive persons starting dolutegravir-based antiretroviral therapy. Clin Infect Dis 2020; 70:1267–74.

24. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. Curr Opin Infect Dis 2020; 33:10–9.

25. Bakal DR, Coelho LE, Luz PM, et al. Obesity following ART initiation is common and influenced by both traditional and HIV ART-specific risk factors. J Antimicrob Chemother 2018; 73:217–85.

26. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. Clin Infect Dis 2020; 71:1379–89.