Integrase Strand Transfer Inhibitors and Weight Gain in Children and Youth With Perinatal Human Immunodeficiency Virus in the DC Cohort

Wei Li A. Koay,[1,2] Sahera Dirajlal-Fargo,[3,4,5] Matthew E. Levy,[6,7] Paige Kulie,[6] Anne Monroe,[6] Amanda D. Castel,[6] and Natella Y. Rakhmanina[1,2,8]; for the DC Cohort Executive Committee

[1]Department of Infectious Diseases, Children's National Hospital, Washington, District of Columbia, USA, [2]School of Medicine and Health Sciences, George Washington University, Washington, District of Columbia, USA, [3]School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA, [4]University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA, [5]Pediatric Infectious Diseases, Rainbow Babies and Children's Hospital, Cleveland, Ohio, USA, [6]Milken Institute School of Public Health, George Washington University, Washington, District of Columbia, USA, [7]Westat, Rockville, Maryland, USA, and [8]Elizabeth Glaser Pediatric AIDS Foundation, Washington, District of Columbia, USA

We conducted a retrospective analysis of 38 children and youth with human immunodeficiency virus (aged 0–19 years) in the United States and report an increased rate of change of BMI-for-age z score after initiating integrase strand transfer inhibitors (+0.19 z score units/year [95% confidence interval, .01–.37]; P = .036) for a median follow-up of 527.5 days.

Keywords. adolescents; body mass index; HIV; integrase inhibitors; youth.

Integrase strand transfer inhibitor (INSTI) use has become widespread for pediatric and adolescent antiretroviral treatment (ART). The INSTI dolutegravir (DTG) is recommended as the preferred first- and second-line antiretroviral drug by the World Health Organization (WHO) for adults and children with human immunodeficiency virus (HIV) [1, 2], following recent approval of DTG for infants and young children weighing ≥3 kg starting at 4 weeks of age [3].

Several large cohort studies in adults with HIV have shown that INSTI-based regimens, particularly with DTG, are associated with weight gain and metabolic complications [4–9], while other studies have shown no overall change in weight gain on INSTI-based regimens [10–12]. The mechanisms for weight

gain for individuals on ART are likely multifactorial including ART regimen, sex, race, baseline HIV RNA viral load (VL) and CD4 cell count, inflammation, reduction in metabolic requirements, diet, and physical activity [13, 14].

To date, 2 studies have reported an increase in body mass index (BMI) in children and adolescents living with HIV up to 96 weeks after switching to DTG-based ART in Africa, Asia, and Europe [15, 16]. BMI-for-age z score (BMI relative to the population median BMI in z score units) [17] measures relative weight change adjusted for age and sex, and is the optimal tool to evaluate annual adiposity changes for children [18]. In this study, we examined individual BMI-for-age z score trajectories following initiation of an INSTI-based regimen in children and youth, defined as young persons living with HIV (YPHIV), within an observational clinical cohort in the United States (US).

METHODS

Study Population

The DC Cohort study is an observational longitudinal clinical cohort of persons with HIV who receive their HIV care within 15 clinics in Washington, District of Columbia [19]. The protocol was approved by the George Washington University Institutional Review Board (IRB number 071029), which serves as the IRB of record for the majority of the sites in the study.

For this retrospective analysis, data were collected between January 2011 and March 2019. YPHIV were included if they were aged 2–19 years at the time of INSTI initiation and initiated an INSTI-based regimen (raltegravir [RAL], elvitegravir [EVG], DTG, or bictegravir [BIC]) while enrolled in the cohort. YPHIV were included if they had ≥2 weights recorded ≥6 months apart within the 2 years both pre– and post–INSTI initiation. Weights were considered only if there was a height measurement within 6 months before the weight measurement.

Measures

"INSTI initiation" was defined as new prescription data for RAL, EVG, DTG, or BIC with no evidence of prior use of any INSTI. "Post-INSTI" describes the time after INSTI initiation while still receiving INSTIs. We used all available BMI-for-age z score measurements within 2 years pre–/post–INSTI initiation. The covariates of interest included age and BMI at INSTI initiation, sex, race/ethnicity, mode of HIV acquisition, most recent CD4 cell count and HIV VL within 6 months of INSTI initiation, smoking history, and current prescription for weight-influencing medication (including hormones, anti-lipemics, and appetite stimulants/suppressants).

Statistical Analysis

Descriptive statistics were summarized using median and interquartile range (IQR) for continuous variables, and frequency and percentage for categorical variables. We compared the slopes of BMI-for-age z score trajectories post– vs pre–INSTI initiation using piecewise linear mixed-effects models with an unstructured correlation matrix. The random effects in the model were a random intercept and the slopes pre– and post–INSTI initiation. We adjusted for BMI-for-age z score at INSTI initiation and all covariates listed in the "Measures" section. P values < .05 were considered statistically significant. Analyses were conducted using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Participant Characteristics

Table 1 describes the characteristics of the 38 participants who were included in this analysis. Participants had a median age of 15 (IQR, 11–16) years and the majority (61%) were 13–19 years of age. One-third of the participants were male (37%), and the majority were non-Hispanic black (95%) and had perinatally acquired HIV (92%). Only 1 participant was ART naive. At INSTI initiation, 42% of participants had an undetectable HIV VL and a median CD4 count of 697 (IQR, 503–862) cells/μL. More than half of the participants (55%) had a normal BMI (18.5–24.9 kg/m²) at INSTI initiation. Twenty-eight participants were initiated on DTG (74%), 7 on EVG (18%), 3 on RAL (8%), none on BIC, and 9 (24%) on tenofovir alafenamide fumarate (TAF). Two participants were on weight-influencing medications.

Trajectory of BMI-for-Age z Score Change Pre-/Post-INSTI

This analysis included 446 BMI-for-age z score measurements among 38 participants. The median follow-up time on INSTIs was 527.5 (IQR, 477–625) days. Adjusting for all covariates of interest, the mean rate of change in BMI-for-age z score was stable during the period pre–INSTI initiation (+0.02 z score units/year [95% confidence interval {CI}, –.09 to .13]; P = .72); however, mean BMI-for-age z score increased +0.21 z score units/year during the period post–INSTI initiation (95% CI, .08–.35, P = .0027; +0.15 z score units/year [95% CI, .0004–.31], P = .0049 excluding participants on TAF) (data not shown). The adjusted difference in the mean rate of change in BMI-for-age z score post– vs pre–INSTI initiation was +0.19 z score units/year (95% CI, .01–.37, P = .036; +0.14 z score units/year [95% CI, –.06 to .34], P = .17 excluding participants on TAF) (Figure 1). Preswitch regimen with a protease inhibitor (PI) or nonnucleoside reverse transcriptase inhibitor (NNRTI) was not associated with change in BMI (P ≤ .27).

DISCUSSION

This study contributes to a knowledge gap regarding weight changes related to INSTI use in YPHIV and suggests that,

Table 1. Characteristics of Participants Aged 2–19 Years Who Newly Initiated Integrase Strand Inhibitor–Based Regimens, January 2011 to March 2019 (N = 38)

Characteristic	No. (%)
Demographic characteristics	
Age, y, median (IQR)	15 (11–16)
Age category, y	
2–12	15 (39)
13–19	23 (61)
Male sex	14 (37)
Non–Hispanic black	36 (95)
HIV infection and ART characteristics	
Perinatally acquired HIV	35 (92)
Undetectable HIV VL (<20 copies/mL) at INSTI initiation	16 (42)
Nadir CD4 count, cells/μL, median (IQR)	225 (54–376)
CD4 count at INSTI initiation, cells/μL, median (IQR)	697.5 (503–862)
CD4 %, median (IQR)	30.5 (19–34)
Follow-up time on INSTIs, d, median (IQR)	527.5 (477–625)
Prior ART regimen	
PI based	26 (68)
NNRTI based	6 (16)
EFV	3 (8)
NVP	3 (8)
NRTI only	4 (10)
NNRTI/PI based	1 (3)
ART naive	1 (3)
Initiated INSTI	
DTG	28 (74)
EVG	7 (18)
RAL	3 (8)
Regimen with TAF	9 (24)
Anthropometric characteristics	
Height, m, median (IQR)	1.60 (1.52–1.65)
Height-for-age z score, median (IQR)	–0.50 (–1.21 to –0.05)
Weight, kg, median (IQR)	57.61 (49.44–64.86)
Weight-for-age z score, median (IQR)	0.41 (–0.47 to 1.11)
BMI-for-age z score, median (IQR)	0.86 (–0.06 to 1.26)
BMI, kg/m², median (IQR)	22.68 (20.11–25.80)
BMI category, kg/m²	
Underweight (<18.5)	3 (8)
Normal (18.5–<24.9)	21 (55)
Overweight (25–29.9)	13 (34)
Obese (≥30)	1 (3)
Prescription for weight-influencing medication	2 (5)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir; TAF, tenofovir alafenamide fumarate; VL, viral load.

similar to adults with HIV, predominantly treatment-experienced YPHIV have evidence of higher BMI-for-age z score trend following INSTI initiation. Despite this increased trajectory of BMI-for-age z score after INSTI initiation, the average BMI-for-age z score at the end of the study period was reassuringly between 0 and 1, where 1 is the cutoff used to
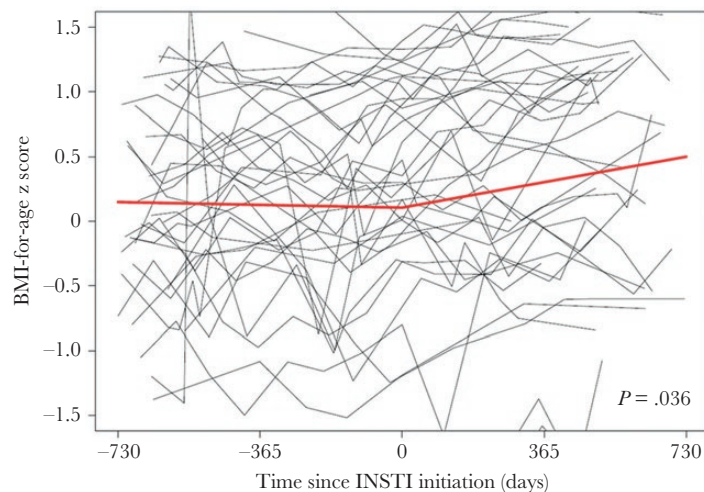
Figure 1. Spaghetti plot of all body mass index (BMI)–for-age z score measurements, with piecewise linear regression line, pre– and post–integrase strand transfer inhibitor (INSTI) initiation among DC Cohort participants aged 2–19 years (446 BMI-for-age z score measurements among 38 participants). The P value represents a test of a difference in slope between the 2 years pre– and post–INSTI initiation, adjusting for BMI at INSTI initiation, age at INSTI initiation, sex, race/ethnicity, mode of human immunodeficiency virus (HIV) acquisition, most recent CD4 count (cells/μL; time-updated), and most recent HIV viral load (time-updated), smoking status, and current prescription for weight-influencing medication (time-updated).

categorize children at risk for being overweight by the WHO [20]. Additionally, differences in weight gain between ART regimens may be associated with a return-to-health phenomenon, seen in advanced HIV [7, 21, 22]. However, the increased BMI-for-age z score trajectory seen in treatment-experienced YPHIV post-INSTI was adjusted for multiple covariates including CD4 count and VL, and may not represent a mere return to health.

Although weight gain on ART may be beneficial, there might be a tipping point at which excessive weight is associated with negative health outcomes [14]. It has been well documented in large population studies that even slight BMI increases in childhood can be associated with cardiovascular disease and metabolic disease in adulthood [23, 24]. Our participants were predominantly black, a population that is disproportionately affected by cardiovascular disease [25]. Most YPHIV in this analysis had perinatally acquired HIV, and represent a population that may be at higher risk for INSTI-associated changes in BMI [10, 26]. Youth with perinatally acquired HIV are known to have higher rates of metabolic and vascular comorbities compared to their uninfected peers, those with horizontally acquired HIV or HIV-exposed uninfected youth [27–29]. Despite adjusting our analysis for variables that are known to be associated with weight gain in adults with HIV including sex, race, baseline BMI, and smoking history [30–32], the persistent increase in BMI-for-age z score observed in YPHIV is concerning. Our study represents US children and youth who are already burdened by high rates of obesity and metabolic disease [33].

Data on randomized trials in YPHIV on INSTI in resource-limited settings are lacking; however, recent results from ODYSSEY, an open-label randomized clinical trial among YPHIV from predominantly African countries, suggested a slight but significant increase in BMI at week 96 among YPHIV on DTG-based ART compared to those on PI- or NNRTI-based ART [16]. In adults, history of being on PIs [34] and TAF [6, 35] has been associated with a higher risk of weight gain. After excluding participants on TAF, there was still a significant increase in BMI-for-age z score post–INSTI initiation. In future analyses, we plan to further examine the association between TAF-based regimens and BMI trajectory among YPHIV.

Our study had limitations. First, due to the small number of participants, we were underpowered to detect differences based on sex or race. We did not have information on medication adherence; however, we used VL as a surrogate marker. We were unable to adjust for sexual maturity, the type of weight gain (fat vs lean mass), and different regional fat distribution (truncal vs peripheral), as these measures were not collected. We did not have a control group of YPHIV with non-INSTI regimens due to limited number of YPHIV on non-INSTI regimens in the DC Cohort during the study period. However, our study showed similar trends in BMI-for-age z score to European and North American studies in children and youth living with HIV, which reported increased BMI-for-age z score after 2–4 years on ART, suggesting that our findings may be consistent with expected anthropometric changes in YPHIV receiving ART [36, 37]. Despite these limitations, a major strength of this study is the longitudinal cohort with reliable anthropometric data, which allowed us to evaluate BMI trajectory pre- and post-INSTI in YPHIV in the US.

CONCLUSIONS

Predominantly perinatally infected YPHIV in this US cohort had an increased trajectory of weight gain after initiating

INSTIs compared to weight gain before INSTI initiation. The increased rate of change in BMI-for-age z score may be multifactorial, including use of INSTIs. This study highlights the importance of BMI monitoring in YPHIV and the need for better understanding of the implications of ART choice on BMI in YPHIV.

Notes

References

1. World Health Organization. Update of recommendations on first–and second–line antiretroviral regimens 2019. https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1. Accessed 28 October 2019.

2. World Health Organization. Updated Recommendations on HIV Prevention, Infant Diagnosis, Antiretroviral Initiation and Monitoring: March 2021. Geneva, Switzerland: WHO; **2021**.

3. US Food and Drug Administration. FDA news release: FDA approves drug to treat infants and children with HIV 2020. https://www.fda.gov/news-events/press-announcements/fda-approves-drug-treat-infants-and-children-hiv. Accessed 1 July 2020.

4. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment-naive persons starting dolutegravir-based antiretroviral therapy. Clin Infect Dis **2020**; 70:1267–74.

5. Kerchberger AM, Sheth AN, Angert CD, et al. Weight gain associated with integrase stand transfer inhibitor use in women. Clin Infect Dis **2020**; 71:593–600.

6. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. N Engl J Med **2019**; 381:803–15.

7. 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.

8. Lamorde M, Atwiine M, Owarwo NC, et al. Dolutegravir-associated hyperglycaemia in patients with HIV. Lancet HIV **2020**; 7:e461–2.

9. Kileel E, Lo JM, C, Zanni MV, et al. Assessment of obesity and metabolic profile by integrase inhibitor use in REPRIEVE [abstract 506]. In: Conference on Retroviruses and Opportunistic Infections, Virtual Meeting; **2021**.

10. Taramasso L, Di Biagio A, Bovis F, et al. Switching to integrase inhibitors unlinked to weight increase in perinatally HIV-infected young adults and adolescents: a 10-year observational study. Microorganisms **2020**; 8:864.

11. Guaraldi G, Calza S, Milic J, et al. Dolutegravir is not associated with weight gain in antiretroviral therapy experienced geriatric patients living with HIV. AIDS **2021**; 35:939–45.

12. Podzamczer D, Mican R, Tiraboschi JM, et al. D/C/F/TAF vs DTG/ABC/3TC for initial treatment in HIV+ adults: a randomized study [abstract 431]. In: Conference on Retroviruses and Opportunistics Infections, Virtual Meeting; **2021**.

13. Achhra AC, Mocroft A, Reiss P, et al; D:A:D Study Group. Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. HIV Med **2016**; 17:255–68.

14. Erlandson KM, Lake JE. Fat matters: understanding the role of adipose tissue in health in HIV infection. Curr HIV/AIDS Rep **2016**; 13:20–30.

15. Thivalapill N, Simelane T, Mthethwa N, et al. Transition to dolutegravir is associated with an increase in the rate of BMI change in a cohort of virally suppressed adolescents [manuscript published online ahead of print 29 October 2020]. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa1652.

16. Turkova A; ODYSSEY/PENTA–20 Trial Team. Dolutegravir-based ART is superior to NNRTI/PI-based ART in children and adolescents [abstract 174]. In: Conference on Retroviruses and Opportunistic Infections, Virtual Meeting; **2021**.

17. Centers for Disease Control and Prevention. Growth chart training 2019. https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. Accessed 1 July 2019.

18. Inokuchi M, Matsuo N, Takayama JI, Hasegawa T. BMI z-score is the optimal measure of annual adiposity change in elementary school children. Ann Hum Biol **2011**; 38:747–51.

19. Greenberg AE, Hays H, Castel AD, et al; DC Cohort Executive Committee. Development of a large urban longitudinal HIV clinical cohort using a web-based platform to merge electronically and manually abstracted data from disparate medical record systems: technical challenges and innovative solutions. J Am Med Inform Assoc **2016**; 23:635–43.

20. World Health Organization. Training Course on Child Growth Assessment: WHO Child Growth Standards. Geneva, Switzerland: WHO; **2008**.

21. Erlandson KM, Kitch D, Tierney C, et al. Weight and lean body mass change with antiretroviral initiation and impact on bone mineral density. AIDS **2013**; 27:2069–79.

22. Bares SH, Smeaton LM, Xu A, et al. HIV-infected women gain more weight than HIV-infected men following the initiation of antiretroviral therapy. J Womens Health (Larchmt) **2018**; 27:1162–9.

23. Baker JL, Olsen LW, Sørensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. N Engl J Med **2007**; 357:2329–37.

24. Viitasalo A, Pitkänen N, Pahkala K, et al. Increase in adiposity from childhood to adulthood predicts a metabolically obese phenotype in normal-weight adults. Int J Obes (Lond) **2020**; 44:848–51.

25. Jolly S, Vittinghoff E, Chattopadhyay A, Bibbins–Domingo K. Higher cardiovascular disease prevalence and mortality among younger blacks compared to whites. Am J Med **2010**; 123:811–8.

26. Li J, Yusuf EH, Agwu AL. Excessive weight gain associated with dolutegravir initiation in a 10-year-old female with perinatally acquired human immunodeficiency virus: a case report and review of the literature. J Pediatric Infect Dis Soc **2021**; 10:373–75.

27. Dirajlal–Fargo S, Sattar A, Kulkarni M, et al. HIV-positive youth who are perinatally infected have impaired endothelial function. AIDS **2017**; 31:1917–24.

28. Sharma TS, Somarriba G, Arheart KL, et al. Longitudinal changes in body composition by dual-energy radiograph absorptiometry among perinatally HIV-infected and HIV-uninfected youth: increased risk of adiposity among HIV-infected female youth. Pediatr Infect Dis J **2018**; 37:1002–7.

29. Arrive E, Viard JP, Salanave B, et al; ANRS CO19 COVERTE and ENNS Study Groups. Metabolic risk factors in young adults infected with HIV since childhood compared with the general population. PLoS One **2018**; 13:e0206745.

30. McComsey GA, Eron JJ, Santiago S, et al. Weight gain during treatment among 3,468 treatment-experienced adults with HIV [abstract 671]. In: Conference on Retroviruses and Opportunistic Infections, Seattle, WA; **2019**.

31. Lake JE, Wu K, Bares SH, et al. Risk factors for weight gain following switch to integrase inhibitor–based antiretroviral therapy. Clin Infect Dis **2020**; 71:e471–7.

32. Tian J, Venn A, Otahal P, Gall S. The association between quitting smoking and weight gain: a systematic review and meta-analysis of prospective cohort studies. Obes Rev **2015**; 16:883–901.

33. Sanyaolu A, Okorie C, Qi X, et al. Childhood and adolescent obesity in the United States: a public health concern. Glob Pediatr Health **2019**; 6:2333794X19891305.

34. Bedimo R, Li X, Adams–Huet B, et al. Differential BMI changes following PI- and INSTI-based ART initiation by sex and race [abstract 675]. In: Conference on Retroviruses and Opportunistic Infections, Seattle, WA; **2019**.

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

36. Melvin AJ, Warshaw M, Compagnucci A, et al. Hepatic, renal, hematologic, and inflammatory markers in HIV-infected children on long-term suppressive antiretroviral therapy. J Pediatric Infect Dis Soc **2017**; 6:e109–15.

37. Schomaker M, Leroy V, Wolfs T, et al; IeDEA West and Southern Africa Regional Collaborations and COHERE in EuroCoord. Optimal timing of antiretroviral treatment initiation in HIV-positive children and adolescents: a multiregional analysis from Southern Africa, West Africa and Europe. Int J Epidemiol **2017**; 46:453–65.