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MAJOR ARTICLE

One in 10 Virally Suppressed Persons With HIV in The Netherlands Experiences ≥10% Weight Gain After Switching to Tenofovir Alafenamide and/or Integrase Strand Transfer Inhibitor

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Background. We determined the frequency of and factors associated with ≥10% weight gain and its metabolic effects in virally suppressed people with human immunodeficiency virus (PWH) from the Dutch national AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort switching to tenofovir alafenamide (TAF) and/or integrase strand transfer inhibitor (INSTI).

Methods. We identified antiretroviral therapy–experienced but TAF/INSTI-naive PWH who switched to a TAF and/or INSTI-containing regimen while virally suppressed for >12 months. Individuals with comorbidities/comedication associated with weight change were excluded. Analyses were stratified by switch to only TAF, only INSTI, or TAF + INSTI. Factors associated with ≥10% weight gain were assessed using parametric survival models. Changes in glucose, lipids, and blood pressure postswitch were modeled using mixed-effects linear regression and compared between those with and without ≥10% weight gain.

Results. Among 1544 PWH who switched to only TAF, 2629 to only INSTI, and 918 to combined TAF + INSTI, ≥10% weight gain was observed in 8.8%, 10.6%, and 14.4%, respectively. Across these groups, weight gain was more frequent in Western and sub-Saharan African females than Western males. Weight gain was also more frequent in those with weight loss ≥1 kg/year before switching, age <40 years, and those discontinuing efavirenz. In those with ≥10% weight gain, 53.7% remained in the same body mass index (BMI) category, while a BMI change from normal/overweight at baseline to obesity at 24 months postswitch was seen in 13.9%, 11.7%, and 15.2% of those switching to only TAF, only INSTI, and TAF + INSTI, respectively. PWH with ≥10% weight gain showed significantly larger, but small increases in glucose, blood pressure, and lipid levels. Lipid increases were limited to those whose switch included TAF, whereas lipids decreased after switching to only INSTI.

Conclusions. Weight gain of ≥10% after switch to TAF and/or INSTI was common in virally suppressed PWH, particularly in females and those starting both drugs simultaneously. Consequent changes in metabolic parameters were, however, modest.

Keywords. tenofovir alafenamide; antiretroviral therapy switch; integrase strand transfer inhibitor; metabolic parameters; weight gain.

INTRODUCTION

Weight gain has been frequently reported in people with human immunodeficiency virus (PWH) after commencing antiretroviral therapy (ART) that includes tenofovir alafenamide (TAF) and/or integrase strand transfer inhibitors (INSTIs). The ADVANCE study, conducted in ART-naive individuals, demonstrated the most pronounced increase in weight (median of +7.1 kg at 96 weeks) when treatment included both TAF and dolutegravir [1]. One limitation of assessing the effect of TAF or INSTIs on weight in those initiating ART is that weight gain, in part, may reflect "return to health" from the initial suppression of viral replication. This may be absent in PWH who are already virally suppressed when switching to TAF and/or INSTIs, yet the effect of discontinued antiretrovirals (ARVs) on weight needs to be considered.

Black race and female sex have been associated with more absolute weight gain after starting TAF and/or INSTIs, with effects being most pronounced in Black females and when TAF and an INSTI were combined [2–7]. Other factors associated with greater weight gain are baseline weight (both lower weight [7–

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10] and obesity [4, 6]), CD4 count <200 cells/μL [3, 7, 8], and age (both younger [10, 11] and older [2, 4] age). In addition, 1 study including both ART-naive and ART-experienced PWH starting dolutegravir found that ART-naive individuals had a greater risk of ≥10% weight gain [8]. Last, certain polymorphisms in the *CYP2B6* gene, leading to differences in efavirenz (EFV) plasma levels [12], can affect weight in PWH starting EFV-based ART. Weight loss was observed in *CYP2B6* slow metabolizers on EFV and weight gain similar to dolutegravir in those with an extensive metabolizer phenotype [13]. This association was also found when switching from EFV to an INSTI, with slow metabolizers gaining significantly greater amounts of weight [14]. This suggests that EFV levels may mitigate weight changes, whereby discontinuing efavirenz could lead to a gain in weight among slow metabolizers.

There may also be a subset of individuals prone to gaining more extreme amounts of weight when exposed to TAF and/or an INSTI, and who may possibly suffer greater metabolic consequences. Studies examining weight gains of more than 7% or 10%, for example, have not all been restricted to virally suppressed individuals [7, 8, 15] or to those being exposed to only TAF, only an INSTI and both simultaneously [10, 15, 16].

The aim of our study therefore was to determine, in a nationally representative population of ART-experienced and virally suppressed PWH in the Netherlands, the proportion of individuals who gained ≥10% in weight after switching to only TAF, only an INSTI, or both combined. We also assessed the factors associated with ≥10% weight gain and examined the impact of weight gain on glucose, lipids, and blood pressure.

METHODS

Study Population

Human immunodeficiency virus (HIV) care in the Netherlands is provided by 24 treatment centers. The HIV Monitoring Foundation (https://www.hiv-monitoring.nl/en) has been prospectively collecting data on demographics, ART, and other clinically relevant characteristics from PWH in the Netherlands from 1998 onward, known as the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort [17]. Data collection is continuous and all data until 27 February 2020 (first COVID-19 diagnosis in the Netherlands) were used.

We identified ART-experienced adults (≥18 years) who were virally suppressed for ≥12 months (isolated HIV type 1 [HIV-1] RNA <200 copies/mL allowed) and switched to TAF- and/or INSTI-containing ART. Participants were TAF- and INSTI- naive prior to switch, while allowing <90 days of previous exposure. Individuals with >90 days' exposure to TAF and/or INSTI and with at least 1 available weight measurement ≤24 months prior to switching and 1 weight measurement ≥3 months after switching, but prior to censoring, were included. Individuals who at the time of switch used medication (corticosteroids, antidepressants, or antipsychotics) or developed conditions associated with weight gain (hypothyroidism, Cushing's syndrome, congestive heart failure, renal failure [including those on hemo- or peritoneal dialysis] or liver cirrhosis) were excluded [18]. We also excluded individuals in whom any of these conditions were diagnosed after switching ART. These conditions could predispose individuals to weight gains prior to switch that are unlikely to be attributed to switching ART. Females who were pregnant at the time of switch were also excluded.

Data Collection

Baseline demographic characteristics included sex at birth, age, region of origin, and years since HIV diagnosis and since first initiation of ART. Time-updated data from routine care included height, weight, blood pressure, smoking behavior, alcohol consumption, CD4/CD8 cell counts, HIV-1 RNA, glucose and lipid levels (total cholesterol, high-density lipoprotein [HDL] and low-density lipoprotein [LDL] cholesterol, and triglycerides), any changes in ART, comedication, and incident relevant comorbidities.

Region of origin was categorized as Europe, North America, Australia, and New Zealand (recategorized as "Western"); sub-Saharan Africa; Latin America and the Caribbean; East and Southeast Asia; and other. Weight gain prior to switch was calculated as the mean change in weight prior to switch in kilograms per year. Smoking and alcohol consumption were categorized as never/former/current and changes as no change/stopped/started.

Hypertension, diabetes mellitus, and metabolic syndrome were defined according to criteria established by the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study [19]; diagnosis of lipodystrophy was reported by a healthcare provider.

Patient Consent

At its inception, the ATHENA cohort was approved by the institutional review boards of all participating HIV treatment centers. After being informed by their treating physician of the purpose of data and sample collection, individuals can opt out. For our analysis, only existing data have been used and therefore no additional review or consent was required [17].

Statistical Analysis

Analyses were stratified according to whether individuals (1) switched to a TAF-containing regimen; (2) switched to an INSTI-containing regimen; or (3) switched simultaneously to both a TAF- and INSTI-containing regimen (TAF + INSTI). Baseline was defined as the date of switching. Two follow-up periods were defined: (1) prebaseline (<36 months prior to baseline while on suppressive ART); and (2) postbaseline

(from baseline until the date of pregnancy, virological failure, use of medication associated with weight gain, discontinuing ART >3 months [including discontinuation of either TAF or INSTI for individuals who switched to TAF and INSTI], switching to INSTI-based ART [for those in the TAF-containing group], switching to TAF-containing ART [for those in the INSTI-containing group], last available weight measurement, death, or 24 months, whichever occurred first). Switches within the INSTI class were allowed. Time was analyzed in discrete intervals of 6 months before and after baseline, with each visit assigned to the closest 6-month date from switch. Missing data were imputed with the most recent values (ie, last observation carried forward).

Participant characteristics at baseline were compared using Pearson χ^2 test for categorical variables or Kruskal-Wallis test for continuous variables. The most recent weight, blood pressure, and laboratory values obtained ≤24 months prebaseline period were used as baseline measurements. Mean weight change in kilograms per year prebaseline was calculated from a linear regression model fit to each individual, including weight measurements during a maximum period of 36 months prior to baseline. The main outcome was ≥10% gain in weight postbaseline compared to baseline. Weight change in those with ≥10% weight gain was modeled using mixed-effects linear regression, with random intercept for individuals and random slope for discrete time (modeled using restricted cubic splines with 5 knots). Mean weight changes were adjusted for baseline age, baseline weight, sex, and region of origin, and mean change at 24 months postbaseline was compared between groups using a 2-sample *t* test.

The discrete time to ≥10% weight gain postbaseline was modeled using a parametric survival model with Weibull survival distribution and robust variance estimations. The univariable hazard ratio and 95% confidence intervals (CIs) were calculated across levels of time-constant and time-updated covariates. All univariable analyses were adjusted for baseline weight. The multivariable model was built using backward elimination, including all variables associated with a $P < .20$ in univariable analyses and subsequently removing all those with a $P \geq .05$, while forcing baseline body mass index (BMI), age, region of origin, and sex. Biologically plausible interactions between variables were also assessed. Interaction terms were only included in the final model if their addition resulted in better fit, based on the likelihood-ratio test.

Last, the postbaseline changes in glucose, lipids, and blood pressure were determined in all included participants. Mean changes within 24 months postbaseline were modeled using linear regression with random intercept for individuals and random slope for discrete time, and a priori adjusted for baseline age; baseline weight; sex; region of origin; baseline glucose, lipids, or blood pressure; and use of antidiabetics, lipid-lowering agents, or antihypertensive agents at baseline and initiation or discontinuation of these medications postbaseline. Predicted values and standard errors were calculated and used to report mean change in glucose, lipid levels, and blood pressure at 24 months postbaseline with 95% CI. Mean changes at 24 months were compared between those with or without ≥10% weight gain using a 2-sample *t* test.

Statistical significance was defined as 2-sided $P < .05$. Statistical analyses were carried out using Stata/IC version 15.1 (StataCorp, College Station, Texas) and R version 4.1.1 (R Project for Statistical Computing, Vienna, Austria) software.

RESULTS

Description of the Study Population

A total of 6324 ART-experienced PWH without prior exposure to TAF and INSTI switched to a TAF- and/or INSTI-based regimen between May 2007 and November 2019, while having been virally suppressed for at least 12 months. Of those, 829 people were excluded because of using predefined comedications or having predefined comorbidities at moment of switch or developing such comorbidities after switch. Another 404 were censored prior to their first weight measurement after switch and therefore also excluded (Supplementary Figure 1). This resulted in 5091 PWH included in the analysis, of whom 1544 switched to a TAF-, 2629 to an INSTI-, and 918 to a combined TAF- and INSTI-containing regimen.

Median prebaseline follow-up was 30 months (interquartile [IQR], 24–36 months), 30 months (IQR, 18–36 months), and 30 months (IQR, 18–30 months) in the TAF, INSTI, and TAF + INSTI switch groups, respectively. The median number of prebaseline weight measurements (given that each participant had at most 1 measurement per 6 months) was 4 (IQR, 2–5), 3 (IQR, 2–5), and 3 (IQR, 2–4) per group, respectively. Median postbaseline follow-up was 18 months (IQR, 12–24 months) in TAF-switchers, 24 months (IQR, 18–24 months) in INSTI-switchers, and 24 months (IQR, 12–24 months) in those switching to both INSTI and TAF. At least 24 months of postbaseline follow-up was available in 625 (40.5%), 1688 (64.2%), and 461 (50.2%) individuals, respectively. The median number of postbaseline weight measurements was 2 (IQR, 1–3) for all 3 groups.

The baseline characteristics per group are reported in Table 1. Overall, 84.3% were males, 71.8% originated from Western countries, median age was 49.3 years, and median BMI was 24.2 kg/m^2. The median time since HIV diagnosis and since start of first ART was 10.7 and 8.6 years, respectively.

Weight Gain of ≥10%

Weight gain of ≥10% within 24 months after switch occurred in 136 (8.8%), 279 (10.6%), and 132 (14.4%) of individuals switching to a regimen that included TAF, an INSTI, or TAF + INSTI, respectively. Median time to reaching a weight

Table 1. Baseline Characteristics of Included Participants at Moment of Switch to Tenofovir Alafenamide and/or Integrase Strand Transfer Inhibitor, by Switch Group

Characteristic	Switch to TAF (n = 1544)	Switch to INSTI (n = 2629)	Switch to TAF + INSTI (n = 918)	*P* Value
Male sex at birth	1322 (85.6)	2197 (83.6)	773 (84.2)	.210[a]
Age, y, median (IQR)	51.5 (44.0–58.3)	48.0 (41.3–55.3)	49.7 (41.9–55.5)	<.001[b]
<40	253 (16.4)	575 (21.8)	188 (20.5)	<.001[a]
40–49 y	430 (27.9)	948 (36.1)	277 (30.2)	
50–59 y	541 (35.0)	735 (28.0)	329 (35.8)	
≥60	320 (20.7)	371 (14.1)	124 (13.5)	
Region of origin				.065[a]
Western regions	1131 (73.3)	1888 (71.8)	638 (69.6)	
Sub-Saharan Africa	150 (9.7)	306 (11.6)	99 (10.8)	
Latin America and the Caribbean	166 (10.7)	260 (9.9)	104 (11.3)	
East and Southeast Asia	62 (4.0)	110 (4.2)	39 (4.2)	
Other regions	35 (2.3)	65 (2.5)	38 (4.1)	
HIV characteristics, median (IQR)				
Years since HIV diagnosis	11.7 (7.4–17.5)	9.9 (6.1–15.2)	11.1 (7.4–15.7)	<.001[b]
Years since start of first ART	9.3 (5.8–15.7)	7.9 (4.6–13.6)	8.7 (5.8–14.2)	<.001[b]
Prior years with UDT viral load	7.2 (4.6–11.0)	5.8 (3.3–9.4)	7.1 (4.5–10.0)	<.001[b]
CD4 count, cells/μL	665 (520–845)	630 (485–798)	690 (525–864)	<.001[b]
CD8 count, cells/μL	827 (630–1080)	847 (638–1100)	807 (622–1098)	.250[b]
CD4/CD8 ratio	0.82 (0.60–1.13)	0.76 (0.54–1.06)	0.84 (0.61–1.12)	.001[b]
Weight, kg, median (IQR)	78.0 (69.0–86.8)	76.0 (67.9–85.0)	78.0 (68.9–87.0)	<.001[b]
BMI, kg/m^2, median (IQR)	24.4 (22.3–26.8)	24.1 (21.8–26.7)	24.3 (22.3–27.0)	.003[b]
BMI category[c]				
Underweight	44 (2.8)	89 (3.4)	27 (2.9)	.310[a]
Normal weight	831 (53.9)	1481 (56.3)	489 (53.3)	
Overweight	519 (33.6)	831 (31.6)	305 (33.2)	
Obese	150 (9.7)	228 (8.7)	97 (10.6)	
Weight change prebaseline, kg/y median (IQR)	0 (−0.67 to +1.07)	0 (−0.63 to +1.00)	0 (−0.62 to +1.13)	.800[b]
Type of INSTI				<.001[a]
Raltegravir	NA	525 (20.0)	4 (0.4)	
Elvitegravir	NA	360 (13.7)	778 (84.8)	
Dolutegravir	NA	1744 (66.3)	60 (6.5)	
Bictegravir	NA	0 (0.0)	76 (8.3)	
Change third agent at baseline				<.001[a]
Stop efavirenz	99 (6.4)	840 (32.0)	384 (41.8)	
Stop nevirapine	23 (1.5)	299 (11.4)	126 (13.7)	
Stop darunavir	10 (0.7)	362 (13.8)	149 (16.2)	
Stop atazanavir	66 (4.3)	398 (15.1)	121 (13.2)	
Stop lopinavir	9 (0.6)	163 (6.2)	27 (2.9)	
Stop other NNRTI	10 (0.7)	274 (10.4)	91 (9.9)	
Stop other PI	1 (0.1)	33 (1.3)	5 (0.5)	
No change in PI or NNRTI	1326 (85.9)	257 (9.8)	14 (1.5)	
Unknown	0 (0.0)	3 (0.1)	1 (0.1)	
Change NRTI at baseline				<.001[a]
Stop TDF	1472 (95.3)	979 (37.2)	834 (90.9)	
Stop abacavir	36 (2.3)	91 (3.5)	52 (5.7)	
Stop other NRTI	26 (1.7)	241 (9.2)	19 (2.1)	
No change in NRTI	10 (0.7)	1315 (50.0)	12 (1.3)	
Unknown	0 (0.0)	3 (0.1)	1 (0.1)	
Current smoking[d]	288 (18.7)	647 (24.6)	186 (20.3)	<.001[a]
Current alcohol consumption[e]	421 (27.3)	941 (35.8)	260 (28.3)	<.001[a]
Comorbidities				
Hypertension	339 (22.0)	465 (17.7)	157 (17.1)	<.001[a]
Diabetes mellitus	85 (5.5)	138 (5.2)	37 (4.0)	.250[a]

Table 1. Continued

Characteristic	Switch to TAF (n = 1544)	Switch to INSTI (n = 2629)	Switch to TAF + INSTI (n = 918)	*P* Value
Metabolic syndrome	29 (1.9)	44 (1.7)	19 (2.1)	.720[a]
Lipodystrophy	240 (15.5)	609 (23.2)	144 (15.7)	<.001[a]

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

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NA, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; UDT, undetectable.

[a]Pearson χ^2 test.

[b]Kruskal-Wallis test.

[c]BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30.0 kg/m^2).

[d]Information on smoking unknown in 814/1544, 1022/2629, and 464/918 individuals per switch group, respectively.

[e]Information on alcohol consumption unknown in 956/1544, 1325/2629, and 537/918 individuals per switch group, respectively.

gain of ≥10% was 12 months (IQR, 6–18 months) in each of the 3 groups. Generally, in each group a higher proportion of females than males experienced ≥10% weight gain, which was the case similarly for females from Western or sub-Saharan African regions (Table 2).

Absolute Change in Weight in Those With ≥10% Weight Gain Postbaseline

As shown in Figure 1, the adjusted mean weight gain at 24 months postbaseline was +9.38 kg (95% CI, 7.93–10.83 kg) for those switching to only TAF, +9.59 kg (95% CI, 8.69–10.49 kg) for those switching to only INSTI, and +10.24 kg (95% CI, 8.75–11.74 kg) for those switching to TAF + INSTI. The mean weight gain at 24 months was significantly greater in those switching to TAF + INSTI, compared to those switching to only TAF ($P < .001$) or to only INSTI ($P < .001$). The absolute weight change in all participants per switch group is depicted in Supplementary Figure 2.

Determinants of ≥10% Weight Gain

Among all switch groups, females from Western or sub-Saharan African regions were at increased risk compared to males from Western regions. In addition, weight loss of ≥1 kg/year prebaseline (compared to ≥1 kg/year weight gain) and age <40 years (compared to age ≥60 years) were each also associated with a significantly higher risk of ≥10% weight gain (Table 3; univariable analyses in Supplementary Tables 1–3). There were no significant interactions in any of the final multivariable models.

In addition, among individuals switching to only TAF, being underweight at baseline (compared to normal weight) and having a higher baseline CD8 cell count were also associated with a higher risk of ≥10% weight gain.

Among individuals switching to only an INSTI, being a current smoker or starting smoking again were additional risk factors, as were discontinuation of EFV or lopinavir.

Among individuals switching to TAF + INSTI, discontinuation of EFV compared to discontinuation of atazanavir was again significantly associated with a higher risk of ≥10% weight gain. There was no association between any particular INSTI and weight increase of ≥10% in univariable analysis, either in the only INSTI group or the TAF + INSTI group.

In a sensitivity analysis, risk factors for ≥7% weight gain were largely similar to those identified for ≥10% weight gain (Supplementary Table 4), although change in smoking behavior in individuals switching to an INSTI-based regimen was no longer associated with ≥7% weight gain in the multivariable model. Discontinuation of abacavir (compared to discontinuing tenofovir disoproxil fumarate [TDF]) was associated with a higher risk of ≥7% weight gain in those switching to only TAF or only an INSTI, although CIs were wide. In individuals switching to TAF + INSTI, use of dolutegravir vs elvitegravir was associated with an increased risk of ≥7% weight gain.

In an additional sensitivity analysis, we excluded 103 individuals with limited exposure of <90 days to TAF (n = 23) and/or INSTI (n = 92) prior to the switch date in our analyses. We found no differences in the results as compared to the primary analyses.

Change in BMI Category

Supplementary Figure 3 shows the postbaseline change in BMI category in individuals with ≥10% weight gain. Of the 547 participants with ≥10% weight gain, 365 remained in follow-up at 24 months. Of those 365 individuals, 53.7% remained in the same BMI category as at baseline. At 24 months after switch to TAF, INSTI, or TAF + INSTI, 29.2% (n = 21/72), 27.6% (n = 59/214), and 26.6% (n = 21/79), respectively, had a BMI change from normal to overweight and 13.9% (n = 10/72), 11.7% (n = 25/214), and 15.2% (n = 12/79), respectively, had a BMI change from normal or overweight to obesity.

Changes in Glucose, Lipids, and Blood Pressure

At 24 months after switching, minor increases in nonfasting glucose were observed across all 3 switch groups, being more pronounced when the regimen switch included TAF (Table 4). These increases were similar regardless of the degree

Table 2. Number and Proportion of Participants With ≥10% Weight Gain Postbaseline, by Switch Group and Region of Origin, Stratified by Sex

	Switch to TAF (n = 1544)		Switch to INSTI (n = 2629)		Switch to TAF + INSTI (n = 918)	
Characteristic	Male	Female	Male	Female	Male	Female
No. of patients	108/1322 (8.2)	28/222 (12.6)	220/2197 (10.0)	59/432 (13.7)	99/773 (12.8)	33/145 (22.8)
Region of origin						
Western regions	86/1051 (8.2)	10/80 (12.5)	171/1717 (10.0)	24/171 (14.0)	68/590 (11.5)	10/48 (20.8)
Sub-Saharan Africa	2/65 (3.1)	11/85 (12.9)	13/138 (9.4)	22/168 (13.1)	7/43 (16.3)	13/56 (23.2)
Latin America and Caribbean	14/132 (10.6)	2/34 (5.9)	25/216 (11.6)	5/44 (11.4)	12/80 (15.0)	6/24 (25.0)
East and Southeast Asia	2/44 (4.5)	5/18 (27.8)	5/71 (7.0)	7/39 (17.9)	7/29 (24.1)	3/10 (30.0)
Other	4/30 (13.3)	0/5 (0.0)	6/55 (10.9)	1/10 (10.0)	5/31 (16.1)	1/7 (14.3)

All values are No./total No. (%).

Abbreviations: INSTI, integrase strand transfer inhibitor; TAF, tenofovir alafenamide.

of weight change, except for a statistically significantly greater rise in glucose in those who switched to only TAF without ≥10% weight gain ($P = .043$).

Significant increases in nonfasting total and LDL cholesterol as well as triglycerides for those with ≥10% weight gain were only observed when the switch included TAF, but not when switching to only INSTI. After switching to only INSTI, these lipids declined and significantly more so in those who did not gain ≥10% weight. Similar minor increases in systolic and diastolic blood pressure were seen, which, with the exception of diastolic blood pressure in those switching to combined TAF + INSTI, were all statistically significantly greater in those with ≥10% weight gain.

DISCUSSION

In this nationally representative observational cohort study of virally suppressed PWH in the Netherlands, as many as 1 in 10 individuals had ≥10% weight gain after switch to TAF and/or INSTI, and more frequently so in those switching to TAF and INSTI simultaneously. Both Western and sub-Saharan African females were at increased risk after switch to either TAF, INSTI, or TAF + INSTI. Finally, changes in metabolic parameters including blood pressure, albeit modest, were greater in those with than without ≥10% weight gain.

Our study is the first to report occurrence of ≥10% weight gain separately for PWH switching to only TAF, only an INSTI, and combined TAF + INSTI. Previous studies examining the effects on weight in virally suppressed PWH switching to TAF or an INSTI have reported similar overall percentages of ≥10% weight gain as observed in our study during a maximum of 24 months follow-up [10, 20]. Weight gain of ≥10% was not associated with any particular INSTI in our study. However, the distribution of INSTIs switched to was different in the only INSTI group vs the combined TAF + INSTI group, making it difficult to generalize on the activity of any specific INSTI agent.

In line with results from a number of other studies [8, 10, 11, 15], Western and sub-Saharan African females, those younger than 40 years, and those previously losing weight had a significantly higher risk of ≥10% weight gain after switch to either TAF, INSTI, or both. Moreover, those discontinuing EFV (which was the case for approximately one-third of participants starting an INSTI) were at increased risk of ≥10% weight gain after switch to INSTI or TAF + INSTI. This could potentially be driven by individuals with a slow metabolizer phenotype associated with certain *CYP2B6* polymorphisms. As previously

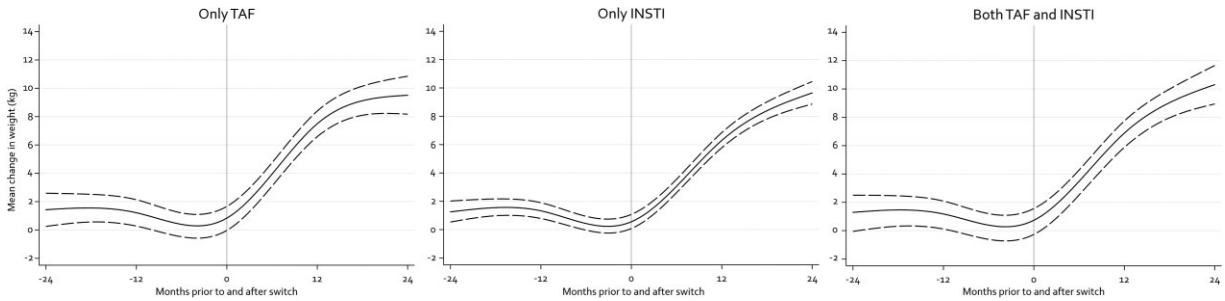

Figure 1. Mean change in weight in the 24 months prior to and after antiretroviral therapy switch in participants with ≥10% weight gain postbaseline after switch to only tenofovir alafenamide (TAF) (n = 136), only integrase strand transfer inhibitor (INSTI) (n = 279), or both TAF and INSTI (n = 132). Mean change in weight in absolute kilograms was adjusted for baseline age, baseline weight, sex, and region of origin. Predicted values and standard errors were calculated and used to plot mean change in weight over time with 95% confidence interval.

Table 3. Factors Associated With ≥10% Weight Gain Within 24 Months Postbaseline (Multivariable Parametric Survival Regression), by Switch Group

	Switch to TAF (n = 1171)[a]		Switch to INSTI (n = 2629)		Switch to TAF + INSTI (n = 918)	
Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Baseline BMI[b]		.003		.027		.046
Underweight	3.17 (1.36–7.38)		1.47 (.88–2.48)		2.10 (.98–4.53)	
Normal weight	Ref		Ref		Ref	
Overweight	0.71 (.44–1.16)		0.75 (.56–1.00)		0.68 (.44–1.05)	
Obese	0.34 (.12–.99)		0.59 (.34–1.02)		0.79 (.41–1.51)	
Baseline age, y		.015		.083		<.001
<40	2.56 (1.21–5.42)		1.19 (.80–1.80)		2.43 (1.22–4.82)	
40–49	1.56 (.80–3.06)		0.78 (.53–1.16)		1.63 (.82–3.23)	
50–59	1.05 (.53–2.11)		0.97 (.65–1.46)		0.84 (.42–1.68)	
≥60	Ref		Ref		Ref	
Subgroup by region of origin		<.001		.169		.054
Western males	Ref		Ref		Ref	
Sub-Saharan African males	0.54 (.14–2.08)		1.07 (.61–1.90)		1.41 (.64–3.15)	
Latin American or Caribbean males	1.02 (.53–1.95)		1.43 (.93–2.21)		1.39 (.73–2.66)	
East or Southeast Asian males	0.32 (.04–2.63)		0.73 (.30–1.75)		1.69 (.71–4.03)	
Males from other regions	2.32 (.67–7.96)		0.86 (.38–1.97)		1.20 (.45–3.21)	
Western females	3.03 (1.49–6.15)		1.63 (1.03–2.58)		2.37 (1.21–4.63)	
Sub-Saharan African females	3.36 (1.45–7.78)		1.84 (1.13–3.02)		3.12 (1.58–6.13)	
Latin American or Caribbean females	0.67 (.09–5.10)		1.60 (.68–3.76)		2.10 (.92–4.80)	
East or Southeast Asian females	2.69 (.61–11.77)		1.81 (.77–4.25)		1.20 (.40–3.60)	
Females from other regions	NS		1.08 (.13–8.77)		1.06 (.12–9.44)	
Weight change prebaseline		<.001		<.001		.004
≥1.0 kg/y weight loss	1.77 (1.04–2.99)		2.50 (1.74–3.61)		2.46 (1.42–4.26)	
0.1–0.9 kg/y weight loss	1.06 (.58–1.95)		1.16 (.76–1.77)		1.42 (.80–2.51)	
0–0.9 kg/y weight gain	0.55 (.30–1.03)		1.12 (.78–1.60)		1.18 (.70–2.01)	
≥1.0 kg/y weight gain	Ref		Ref		Ref	
Change third agent at baseline				.014		<.001
Stop atazanavir	NS		Ref		Ref	
Stop efavirenz	NS		1.63 (1.09–2.44)		2.21 (1.15–4.24)	
Stop nevirapine	NS		1.55 (.95–2.54)		1.77 (.82–3.83)	
Stop darunavir	NS		1.37 (.85–2.22)		1.64 (.78–3.44)	
Stop lopinavir	NS		1.74 (1.03–2.94)		1.69 (.55–5.17)	
Stop other NNRTI	NS		1.11 (.65–1.91)		1.30 (.54–3.09)	
Stop other PI	NS		1.05 (.32–3.42)		1.93 (.15–24.26)	
No change in PI or NNRTI	NS		0.73 (.41–1.30)		1.01 (.10–10.07)	
Unknown	NS		10.18 (.96–108.0)		63.20 (28.52–140.1)	
Baseline CD8 cell count						
(absolute; per 100 cells/μL higher)	1.08 (1.02–1.14)	.004	NS		NS	
Change in smoking behavior postbaseline				.039		
Never	NS		Ref		NS	
No change (former)	NS		0.89 (.45–1.75)		NS	
No change (current)	NS		1.45 (1.04-2.04)		NS	
Stop smoking	NS		1.60 (.88–2.92)		NS	
Start smoking (former)	NS		3.55 (1.48–8.50)		NS	
Start smoking (never)	NS		1.28 (.28–5.84)		NS	
Unknown	NS		1.11 (.82–1.51)		NS	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NS, not significant (thus not included in multivariable model); PI, protease inhibitor; Ref, reference group; TAF, tenofovir alafenamide.

[a]Due to missing CD8 cell counts in 373 individuals, 1171 of 1544 are included in the multivariable model.

[b]BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30.0 kg/m^2).

reported, such individuals are prone to lose weight on EFV and to gain weight after switching away from EFV [13, 14]. The proportion of EFV slow metabolizers is known to be higher among individuals of African descent compared to Caucasians [13, 21], but no correlation has been found between sex and slow metabolizer phenotype [13, 22]. Of note, we did not observe an interaction between ethnicity or sex and discontinuation of EFV in our analyses.

Table 4. Mean Change in Glucose, Lipid Levels, and Blood Pressure at 24 Months After Switch to Only Tenofovir Alafenamide (TAF), Only Integrase Strand Transfer Inhibitor (INSTI), or TAF + INSTI, in Those With and Without ≥10% Weight Gain

	Switch to TAF			Switch to INSTI			Switch to TAF + INSTI		
Laboratory Value	With ≥10% Weight Gain	Without ≥10% Weight Gain	*P* Value	With ≥10% Weight Gain	Without ≥10% Weight Gain	*P* Value	With ≥10% Weight Gain	Without ≥10% Weight Gain	*P* Value[a]
Glucose, mmol/L	+0.20 (−.10 to +.51)	+0.30 (+.13 to +.48)	.041	+0.07 (−.22 to +.36)	+0.07 (−.07 to +.21)	.833	+0.38 (−.31 to +1.06)	+0.25 (+.02 to +.48)	.154
Total cholesterol, mmol/L	+0.64 (+.35 to +.92)	+0.33 (+.24 to +.41)	<.001	−0.12 (−.35 to +.11)	−0.21 (−.29 to −.14)	<.001	+0.46 (+.11 to +.80)	+0.19 (+.06 to +.32)	<.001
HDL cholesterol, mmol/L	+0.10 (−.02 to +.22)	+0.10 (+.06 to +.13)	.336	−0.05 (−.15 to +.05)	−0.01 (−.04 to +.01)	<.001	+0.05 (−.07 to +.16)	+0.09 (+.04 to +.13)	<.001
LDL cholesterol, mmol/L	+0.39 (−.15 to +.93)	+0.19 (+.06 to +.32)	.002	−0.17 (−.48 to +.14)	−0.22 (−.35 to −.10)	.043	+0.49 (+.07 to +.90)	−0.01 (−.23 to +.20)	<.001
Triglycerides, mmol/L	+0.68 (+.31 to +1.05)	+0.41 (+.21 to +.61)	<.001	−0.23 (−.59 to +.14)	−0.30 (−.41 to −.19)	.194	+0.70 (−.34 to +1.74)	+0.10 (−.11 to +.32)	<.001
Systolic BP, mm Hg	+2.78 (−1.77 to +7.32)	+1.71 (+.29 to +3.13)	<.001	+3.29 (−.10 to +6.69)	+0.57 (−.54 to +1.68)	<.001	+2.06 (−2.41 to +6.52)	+0.50 (−1.34 to +2.35)	<.001
Diastolic BP, mm Hg	+3.05 (+.05 to +6.05)	+0.71 (−.19 to +1.61)	<.001	+2.45 (+.20 to +4.71)	+0.53 (−.22 to +1.28)	<.001	+0.43 (−2.56 to +3.41)	+0.42 (−.75 to +1.59)	.984

Values represent mean change with 95% confidence interval at 24 months after switch. Values were predicted using mixed-effects linear regression and are adjusted for baseline age; baseline weight; sex; region of origin; baseline glucose, lipid, or blood pressure values; and use of antidiabetics, lipid-lowering agents, or antihypertensive agents at baseline and initiation and discontinuation of these medications postbaseline.

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; INSTI, integrase strand transfer inhibitor; LDL, low-density lipoprotein; TAF, tenofovir alafenamide.

[a] *P* values were calculated using 2-sample *t* test.

In our study we did not find switching from TDF to TAF to be independently associated with an increased risk of ≥10% weight gain, possibly because the large majority (>90%) who started TAF discontinued TDF. Whether weight gain is related to the removal of the weight-suppressive effect of TDF and/or to a weight-increasing effect of TAF remains unclear. The use of TDF as preexposure prophylaxis was associated with greater odds of 5% weight loss compared to placebo [23], whereas the use of TAF as preexposure prophylaxis was associated with modest weight gain of 1.1 kg after 48 weeks [24]. This suggests that weight gain after switch to TAF may well reflect the composite of both of these independent features.

It remains to be clarified why females in particular are at increased risk of weight gain after start of TAF and/or INSTIs compared to males. Previous studies showed that females have higher plasma concentrations of both EFV [22, 25] and TDF [26, 27], which could cause more weight suppression and subsequently a more pronounced increase in weight when these compounds are discontinued. Higher plasma concentrations in females have also been described for dolutegravir [28] and raltegravir [29], but such data are lacking for other INSTIs. Proposed mechanisms by which INSTIs could increase weight include an effect on adipocyte differentiation, adiponectin, and the central melanocortin system [30, 31].

Mechanisms resulting in higher concentrations of ARVs in females are unclear but could be caused by differences in absorption, distribution, metabolism, and elimination of ARVs, due to sex-specific differences in body composition, sex-related differences in activity of *CYP450* enzymes, or lower renal clearance rates in females compared to males [32, 33]. Females generally have a lower resting energy expenditure (REE, ie, the energy required to keep the body functioning at rest) compared to males [34–36]. The major factor determining REE is lean body mass, which may explain why females—who generally have a lower lean mass and higher fat mass—have lower REE [35–37]. If the effect of TAF and/or INSTIs on weight were to be driven by increased calorie intake, the lower REE in females could explain why weight gain in females would be more pronounced.

Although individuals with ≥10% weight gain in our study showed statistically significantly larger mean changes in blood pressure and lipids than those without ≥10% weight gain, changes were only modest. Similar observations have been reported in individuals with and without ≥10% weight gain commencing dolutegravir [8]. In line with our results, small increases in triglycerides, total cholesterol, and LDL cholesterol following switch to TAF—either with or without an INSTI and irrespective of weight change—have been reported previously [3, 38]. The impact of such minor changes in metabolic parameters on the long-term risk of cardiovascular disease and diabetes remains to be determined.

Our study has a number of strengths. First, the extensive data collection made it possible to analyze a large number

of individuals, while applying strict exclusion and censoring criteria. It also allowed us to separately address ≥10% weight gain in individuals with similar observation time and demographic characteristics who switched to either only TAF, only an INSTI, or to both simultaneously. To the best of our knowledge, this is the first study to do so.

Our study also has several limitations. Weight was measured as part of routine clinical assessment, rather than in a standardized manner and frequency, nor were we able to adjust for lifestyle changes. Finally, adjustment for changes in smoking and alcohol use was imperfect given that time-updated data were missing in a majority of participants.

In conclusion, our nationwide representative cohort of virally suppressed PWH confirmed that a ≥10% gain in weight after switching to TAF and/or an INSTI is common and occurs in approximately 1 in 10 individuals. The pathophysiology underlying such degree of weight gain appears to be multifactorial, with age, sex, the particular drugs being initiated and those being switched away from, and genetic factors influencing drug exposure and metabolism all contributing. Studies focused on individuals susceptible to or experiencing excessive weight gain and that include detailed assessments of body composition and metabolism should be undertaken to unravel its pathophysiology. Long-term follow-up will be required to assess cardiometabolic risk and the benefit of interventions aimed at reversing the weight gain and its metabolic consequences.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. F. W. N. M. W. has served on scientific advisory boards for ViiV Healthcare and Gilead Sciences. P. R. through his institution has received independent scientific grant support from Gilead Sciences, Janssen Pharmaceuticals, Merck & Co, and ViiV Healthcare; and has served on scientific advisory boards for Gilead Sciences, ViiV Healthcare, and Merck & Co, honoraria for which were all paid to his institution. M. v. d. V. through his institution has received independent scientific grant support and consultancy fees from AbbVie, Gilead Sciences, MSD, and ViiV Healthcare, for which honoraria were all paid to his institution. All other authors report no potential conflicts of interest.

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APPENDIX

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Isala, Zwolle: HIV treating physicians: P. H. P. Groeneveld*, J. W. Bouwhuis, A. J. J. Lammers. HIV nurse consultants: A. G. W. van Hulzen, S. Kraan, M. S. M. Kruiper. HIV data collection: G. L. van der Bliek, P. C. J. Bor. HIV clinical virologists/chemists: S. B. Debast, G. H. J. Wagenvoort.

Leids Universitair Medisch Centrum, Leiden: HIV treating physicians: A. H. E. Roukens*, M. G. J. de Boer, H. Jolink, M. M. C. Lambregts, A. H. E. Roukens, H. Scheper. HIV nurse consultants: W. Dorama, N. van Holten. HIV clinical virologists/chemists: E. C. J. Claas, E. Wessels.

Maasstad Ziekenhuis, Rotterdam: HIV treating physicians: J. G. den Hollander*, R. El Moussaoui, K. Pogany. HIV nurse consultants: C. J. Brouwer, D. Heida-Peters, E. Mulder, J. V. Smit, D. Struik-Kalkman. HIV data collection: T. van Niekerk. HIV clinical virologists/chemists: O. Pontesilli, C. van Tienen.

Maastricht UMC+, Maastricht: HIV treating physicians: S. H. Lowe*, A. M. L. Oude Lashof, D. Posthouwer, M. E. van Wolfswinkel. HIV nurse consultants: R. P. Ackens, K. Burgers, J. Schippers. HIV data collection: B. Weijenberg-Maes. HIV clinical virologists/chemists: T. R. A. Havenith, M. van Loo.

Medisch Centrum Leeuwarden, Leeuwarden: HIV treating physicians: M. G. A. van Vonderen*, L. M. Kampschreur. HIV nurse consultants: M. C. van Broekhuizen, S, Faber. HIV clinical virologist/chemist: A. Al Moujahid.

Medisch Spectrum Twente, Enschede: HIV treating physicians: G. J. Kootstra*, C. E. Delsing. HIV nurse consultants: M. van der Burg-van de Plas, L. Scheiberlich.

Noordwest Ziekenhuisgroep, Alkmaar: HIV treating physicians: W. Kortmann*, G. van Twillert*, R. Renckens, J. Wagenaar. HIV nurse consultants and HIV data collection: D. Ruiter-Pronk, F. A. van Truijen-Oud. HIV clinical virologists/chemists: J. W. T. Cohen Stuart, M. Hoogewerf, W. Rozemeijer, J. C. Sinnige.

OLVG, Amsterdam: HIV treating physicians: K. Brinkman*, G. E. L. van den Berk, K. D. Lettinga, M. de Regt, W. E. M. Schouten, J. E. Stalenhoef, J. Veenstra, S. M. E. Vrouenraets. HIV nurse consultants: H. Blaauw, G. F. Geerders, M. J. Kleene, M. Knapen, M. Kok, I. B. van der Meché,

A. J. M. Toonen, S. Wijnands, E. Wttewaal. HIV clinical virologists: D. Kwa, T. J. W. van de Laar.

Radboudumc, Nijmegen: HIV treating physicians: R. van Crevel*, K. van Aerde, A. S. M. Dofferhoff, S. S. V. Henriet, H. J. M. ter Hofstede, J. Hoogerwerf, O. Richel. HIV nurse consultants: M. Albers, K. J. T. Grintjes-Huisman, M. de Haan, M. Marneef. HIV clinical virologist/chemist: F. F. Stelma. HIV clinical pharmacology consultant: D. Burger.

Rijnstate, Arnhem: HIV treating physicians: E. H. Gisolf*, M. Claassen, R. J. Hassing, HIV nurse consultants: G. ter Beest, P. H. M. van Bentum, M. Gelling, N. Langebeek. HIV clinical virologists/chemists: C. M. A. Swanink, M. Klein Velderman.

Spaarne Gasthuis, Haarlem: HIV treating physicians: S. F. L. van Lelyveld*, R. Soetekouw. HIV nurse consultants: L. M. M. van der Prijt, J. van der Swaluw. HIV clinical virologists/chemists: J. S. Kalpoe, A. Vahidnia, A. Wagemakers.

Medisch Centrum Jan van Goyen, Amsterdam: HIV treating physicians: F. N. Lauw, D. W. M. Verhagen. HIV nurse consultant: M. van Wijk.

Universitair Medisch Centrum Groningen, Groningen: HIV treating physicians: W. F. W. Bierman*, M. Bakker, R. A. van Bentum, M. A. van den Boomgaard, J. Kleinnijenhuis, E. Kloeze, A. Middel, D. F. Postma, Y. Stienstra, M. Wouthuyzen-Bakker. HIV nurse consultants: A. Boonstra, H. de Groot-de Jonge, M. M. M. Maerman, P. A. van der Meulen, D. A. de Weerd. HIV clinical virologists/chemists: K. J. van Eije, M. Knoester, C. C. van Leer-Buter, H. G. M. Niesters.

Beatrix Kinderziekenhuis (Universitair Medisch Centrum Groningen), Groningen: HIV treating physicians: E. H. Schölvinck, A. R. Verhage. HIV nurse consultant: H. de Groot-de Jonge. HIV clinical virologists/chemists: M. Knoester, C. C. van Leer-Buter, H. G. M. Niesters.

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