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Risk of Incident Diabetes Mellitus, Weight Gain, and Their Relationships With Integrase Inhibitor–Based Initial Antiretroviral Therapy Among Persons With Human Immunodeficiency Virus in the United States and Canada

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Background. Integrase strand transfer inhibitor (INSTI)–based combination antiretroviral therapy (cART) is associated with greater weight gain among persons with human immunodeficiency virus (HIV), though metabolic consequences, such as diabetes mellitus (DM), are unclear. We examined the impact of initial cART regimen and weight on incident DM in a large North American HIV cohort (NA-ACCORD).

Methods. cART-naive adults (≥18 years) initiating INSTI-, protease inhibitor (PI)–, or nonnucleoside reverse transcriptase inhibitor (NNRTI)–based regimens from January 2007 through December 2017 who had weight measured 12 (±6) months after treatment initiation contributed time until clinical DM, virologic failure, cART regimen switch, administrative close, death, or loss to follow-up. Multivariable Cox regression yielded adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for incident DM by cART class. Mediation analyses, with 12-month weight as mediator, similarly adjusted for all covariates.

Results. Among 22 884 eligible individuals, 47% started NNRTI-, 30% PI-, and 23% INSTI-based cART with median follow-up of 3.0, 2.3, and 1.6 years, respectively. Overall, 722 (3%) developed DM. Persons starting INSTIs vs NNRTIs had incident DM risk (HR, 1.17 [95% CI, .92–1.48]), similar to PI vs NNRTI initiators (HR, 1.27 [95% CI, 1.07–1.51]). This effect was most pronounced for raltegravir (HR, 1.42 [95% CI, 1.06–1.91]) vs NNRTI initiators. The INSTI–DM association was attenuated (HR, 1.03 [95% CI, .71–1.49] vs NNRTIs) when accounting for 12-month weight.

Conclusions. Initiating first cART regimens with INSTIs or PIs vs NNRTIs may confer greater risk of DM, likely mediated through weight gain.

Keywords. HIV; cART; INSTIs; weight; diabetes.

Enhanced weight gain among persons with human immunodeficiency virus (PWH) starting integrase strand transfer inhibitor (INSTI)–based combination antiretroviral therapy (cART) has been reported [1–3]. Weight gain after cART initiation is associated with reduced mortality in underweight and normal-weight individuals [4], but an increasing proportion of PWH become overweight or obese on cART [5, 6]. A higher body mass index (BMI) is associated with greater prevalent diabetes mellitus (DM), neurocognitive impairment, liver disease, and cardiovascular disease among PWH [7–10], and weight gain in the year after cART initiation confers greater risk of incident DM [11, 12].

While weight gain on cART is accompanied by increased risk of metabolic disease, case reports of incident DM and symptomatic hyperglycemia after starting or transitioning to INSTIs [13–15] raise the possibility that INSTIs alter insulin sensitivity independent of weight gain. This theory is supported by findings of increased fibrosis in adipose tissue and reduced insulin sensitivity in adipocytes exposed to INSTIs [16]. An off-target effect of INSTIs on human melanocortin 4 receptor (MC4R), a major regulator of appetite and energy balance, has been hypothesized to contribute to weight gain, though a recent study

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failed to demonstrate any relationship between increased INSTI concentration and MC4R/ligand binding [17].

Weight gain while on cART may contribute to an increased risk of several comorbidities, but the incidence of DM, and its relationship with weight gain, among persons initiating different cART regimens is not well defined. Given the broad adoption of INSTI-based cART as first-line therapy, further data are needed regarding the metabolic effects of these regimens. We therefore examined the impact of initial cART regimen on incident DM, and the potential mediation of this relationship by weight change after cART initiation, among >20 000 cART-naive PWH initiating cART in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

METHODS

Source and Study Populations

The NA-ACCORD collects and harmonizes standardized clinical, demographic, and vital data from >200 clinical and research facilities in the United States (US) and Canada. Institutional review boards at each participating site review and approve the activities of NA-ACCORD [18].

The study population was restricted to cART-naive individuals initiating their first regimen between January 2007 and December 2017, defined as the first uninterrupted cART prescription for ≥45 days to ensure cART initiation and avoid data artifacts. Individuals were considered cART naive if they had no prior cART use and human immunodeficiency virus type 1 (HIV-1) RNA at treatment initiation was detectable (≥400 copies/mL). Individuals with prevalent DM at cART initiation (defined consistently with the primary outcome, described below) were excluded [19].

Exposure of Interest

The exposure was the initial cART regimen core class prescribed: INSTI- or protease inhibitor (PI)–based compared to nonnucleoside reverse transcriptase inhibitor (NNRTI)–based therapy [20]. We further classified initial INSTI-based cART by specific INSTI: dolutegravir, elvitegravir, or raltegravir; bictegravir was excluded as few individuals received it during the study period. Eligible cART regimens included ≥3 active antiretroviral agents. Inclusion was based on the number at each site receiving cART by class or else by core agent (raltegravir, dolutegravir, or elvitegravir): ≥50 individuals in each case.

Outcome of Interest

The primary outcome was initial clinical occurrence of DM after cART initiation. DM was defined by evidence of hemoglobin A1C (HbA1c) ≥6.5%, initiation of diabetes-specific medication, or new DM diagnosis along with diabetes-related medication (to exclude prediabetes from the outcome) [21]. DM diagnoses were established using physician diagnosis mapped to *International Classification of Diseases, Ninth Revision* codes.

Mediation by Weight

Weight change during the first year after cART initiation was assessed as a potential mediating factor in additional analyses. Individual weights at 12 months (±6 months) after cART initiation were included to examine the attenuation (and therefore magnitude of the direct effect) of the exposure-outcome relationship. Weights were measured in pounds or kilograms at each clinical site during routine care with available clinic equipment. Participants missing weight measurements in this window were excluded from mediation analyses.

Potential Confounders

Age (years), sex assigned at birth (male or female), race/ethnicity (white non-Hispanic or non-white), HIV transmission risk factors (men who have sex with men [MSM], heterosexual contact, injection drug use, or other/unknown), baseline weight (kg), baseline $CD4^+$ count (cells/μL; square-root transformed), baseline HIV-1 RNA ($\log_{10}$ copies/mL), and cART initiation calendar year were adjusted for in multivariable regression models. As use of older nucleoside reverse transcriptase inhibitor (NRTI) agents was scarce in this cohort, we did not adjust for nucleoside backbone differences as a potential confounder.

Follow-up

Individuals contributed time at risk from the date of first cART initiation (the origin) until censored on the date of switching cART regimens (ie, a switch between classes, not including NRTI switches), first instance of virologic failure (HIV-1 RNA >1000 copies/mL, based on World Health Organization recommendations), first of 2 consecutive detectable HIV-1 RNA measurements (each ≥400 copies/mL), administrative cohort close, death, or last encounter before 31 December 2017. In mediation analyses, we excluded persons with incident DM before a 12-month weight measurement and used the date of 12-month weight measurement as the origin.

Statistical Analyses

We used Cox proportional hazards regression models to quantify adjusted relative hazards (HRs) and associated 95% confidence intervals (CIs) for incident DM. We stratified all models (ie, baseline hazards varied) by site. We multiply imputed missing baseline data and used restricted cubic splines to flexibly model continuous covariates (except for calendar year of cART initiation). Models including 3-way interactions between initial cART class, sex, and race/ethnicity were constructed for the primary analysis, though interactions were dropped if not

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significant with a 2-tailed α = .05, and mediation models included 12-month weights as an additional covariate [22].

In sensitivity analyses, we excluded individuals initiating cART regimens containing tenofovir alafenamide (TAF); we also included baseline hepatitis C virus (HCV) infection and opportunistic infection status as potential confounders. Additionally, we constructed cumulative incidence curves using the cause-specific hazards of incident DM accounting for all-cause death as a competing risk [23].

All analyses were completed using R statistical software (version 3.4.4; www.r-project.org). Annotated code is available at biostat.mc.vanderbilt.edu/archivedanalyses.

RESULTS

Among 22 884 eligible individuals categorized by initial cART regimen class, 10 846 (47%) started NNRTIs, 6855 (30%) PIs, and 5183 (23%) INSTIs, with median follow-up of 3.0, 2.3, and 1.6 years, respectively (Table 1). There were appreciable differences in sex, HIV transmission risk, and median age distributions across initial cART class, with younger and disproportionately MSM individuals initiating INSTIs compared to NNRTIs. Those starting INSTIs also had higher baseline $CD4^+$ counts (median 363 [interquartile range, 190–535] cells/μL) and more recent cART initiation (median year, 2014) compared to NNRTI initiators (Table 1), reflecting temporal availability of the different classes. Overall, 722 (3%) developed DM for an unadjusted incidence of 10.7 cases per 1000 persons/year, with a slightly lower proportion of DM cases among INSTI initiators (Table 1). Among those with an incident DM diagnosis, 520 (72%) initiated a DM-related medication, which did not differ across initial cART class.

Restricting to NA-ACCORD contributing cohorts with >50 records for each initial cART core agent, 2921 (13%) individuals were excluded. Among 19 963 (87%) remaining individuals, 4606 (23%) started cART on INSTIs, with 26% starting dolutegravir, 23% raltegravir, and 50% elvitegravir (Table 2). Similar patterns by agent were observed as by class, though raltegravir initiators were older and disproportionately white non-Hispanic, and dolutegravir initiators were younger, had higher baseline median $CD4^+$ counts (396 [interquartile range, 198–594] cells/μL), and were disproportionately MSM compared to NNRTI initiators (Table 2). Approximately 3% (686) of these individuals experienced incident DM, though there was a

Table 1. Characteristics of People Living With Human Immunodeficiency Virus Initiating Antiretroviral Therapy of ≥45 Days' Duration, 2007–2016, in Participating North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) Cohorts (Those With ≥50 Individuals Receiving Each Core Class), Stratified by Class of Regimen Core

Characteristic	Total No.	NNRTI-Based (n = 10 846)		PI-Based (n = 6855)		INSTI-Based (n = 5183)		Combined (N = 22 884)		Interclass *P* Value
Sex assigned at birth	22 884									<.001[a]
Male		0.90	(9800)	0.80	(5514)	0.86	(4464)	0.86	(19 778)	
Female		0.10	(1046)	0.20	(1341)	0.14	(719)	0.14	(3106)	
Race/ethnicity	21 801									.034[a]
White, non-Hispanic		0.40	(4054)	0.38	(2438)	0.39	(1956)	0.39	(8448)	
Non-white		0.60	(6208)	0.62	(4063)	0.61	(3082)	0.61	(13 353)	
HIV transmission risk	22 884									<.001[a]
MSM		0.41	(4400)	0.31	(2135)	0.51	(2639)	0.40	(9174)	
IDU, including MSM/IDU		0.11	(1231)	0.14	(993)	0.08	(394)	0.11	(2618)	
Heterosexual		0.15	(1608)	0.20	(1396)	0.18	(948)	0.17	(3952)	
Other/unknown		0.33	(3607)	0.34	(2331)	0.23	(1202)	0.31	(7140)	
Age[b], y	22 884	42 (31, 51)		41 (31, 50)		37 (28, 48)		41 (31, 50)		<.001[c]
Baseline weight[b], kg	18 976	78 (68, 89)		76 (66, 87)		77 (67, 89)		77 (68, 89)		<.001[c]
Weight at 1 y after ART[b], kg	17 585	80 (70, 91)		79 (69, 91)		80 (70, 93)		80 (70, 92)		.053[c]
Baseline BMI[b], kg/m^2	18 170	25 (22, 28)		25 (22, 28)		25 (22, 29)		25 (22, 28)		<.001[c]
Baseline $CD4^+$ count[b], cells/μL	19 410	315 (182, 454)		260 (105, 406)		363 (190, 535)		309 (159, 461)		<.001[c]
Baseline $\log_{10}$ HIV-1 RNA[b]	18 339	4.6 (4.0, 5.1)		4.7 (4.1, 5.2)		4.6 (4.1, 5.2)		4.6 (4.1, 5.1)		<.001[c]
Year of ART initiation[b]	22 884	2010 (2008, 2012)		2010 (2008, 2012)		2014 (2013, 2016)		2011 (2009, 2013)		<.001[c]
Incident diabetes mellitus	22 884									.007[a]
No		0.97	(10 487)	0.97	(6621)	0.98	(5054)	0.97	(22 162)	
Yes		0.03	(359)	0.04	(234)	0.02	(129)	0.03	(722)	
Follow-up time[b], y	22 976	3.00 (1.19, 5.22)		2.26 (0.92, 4.12)		1.60 (0.79, 2.97)		2.33 (0.98, 4.33)		<.001[c]

Numbers in parentheses after proportions are frequencies. N is the number of nonmissing values.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; IDU, injection drug use; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Pearson χ^2 test.

[b]Median (lower quartile, upper quartile).

[c]Kruskal-Wallis test.

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Table 2. Characteristics of People Living With Human Immunodeficiency Virus Initiating Antiretroviral Therapy of ≥45 Days' Duration, 2007–2016, in Participating North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) Cohorts (Those With ≥50 Individuals Receiving Each Active Agent), Stratified by Active Agent of Regimen Core

Characteristic	Total No.	NNRTI-Based (n = 9982)		PI-Based (n = 5375)		RAL-Based (n = 1081)		DTG-Based (n = 1210)		EVG-Based (n = 2315)		Combined (N = 19 963)		Interagent *P* Value
Sex assigned at birth	20 032													<.001[a]
Male		0.91	(9084)	0.82	(4410)	0.85	(917)	0.86	(1044)	0.89	(2058)	0.88	(17 513)	
Female		0.09	(898)	0.18	(965)	0.15	(164)	0.14	(166)	0.11	(257)	0.12	(2450)	
Race/ethnicity	19 347													<.001[a]
White, non-Hispanic		0.40	(3842)	0.38	(1954)	0.46	(487)	0.38	(446)	0.37	(834)	0.39	(7563)	
Non-white		0.60	(5767)	0.62	(3214)	0.54	(567)	0.62	(740)	0.63	(1427)	0.61	(11 715)	
HIV transmission risk	20 032													<.001[a]
MSM		0.40	(4007)	0.36	(1914)	0.43	(462)	0.60	(725)	0.59	(1357)	0.42	(8465)	
IDU, including MSM/IDU		0.12	(1173)	0.16	(846)	0.13	(139)	0.05	(63)	0.07	(155)	0.12	(2376)	
Heterosexual		0.14	(1405)	0.21	(1147)	0.17	(186)	0.21	(250)	0.19	(436)	0.17	(3424)	
Other/unknown		0.34	(3397)	0.27	(1468)	0.27	(294)	0.14	(172)	0.16	(367)	0.28	(5698)	
Age[b], y	20 032	42 (32, 51)		42 (32, 51)		44 (33, 52)		35 (28, 48)		34 (27, 45)		41 (31, 50)		<.001[c]
Baseline weight[b], kg	16 785	78 (69, 89)		77 (67, 88)		78 (68, 90)		76 (67, 89)		77 (67, 90)		78 (68, 89)		<.001[c]
Weight at 1 y after ART[b], kg	15 234	80 (70, 92)		80 (70, 92)		81 (72, 94)		80 (71, 93)		80 (69, 93)		80 (70, 92)		.087[c]
Baseline BMI[b], kg/m^2	16 186	25 (22, 28)		25 (22, 28)		26 (23, 29)		25 (22, 29)		25 (22, 29)		25 (22, 28)		.006[c]
Baseline CD4$^+$ count[b], cells/μL	16 710	319 (184, 464)		259 (102, 415)		332 (158, 492)		396 (188, 594)		380 (214, 554)		315 (162, 475)		<.001[c]
Baseline $\log_{10}$ HIV-1 RNA[b]	15 711	4.6 (4.0, 5.0)		4.7 (4.1, 5.2)		4.6 (4.0, 5.1)		4.6 (4.1, 5.1)		4.6 (4.1, 5.2)		4.6 (4.1, 5.1)		<.001[c]
Year of ART initiation[b]	20 032	2010 (2008, 2012)		2010 (2008, 2012)		2011 (2010, 2013)		2016 (2015, 2016)		2014 (2014, 2015)		2011 (2009, 2013)		<.001[c]
Incident diabetes mellitus	20 032													.01[a]
No		0.97	(9634)	0.96	(5163)	0.95	(1028)	0.98	(1185)	0.98	(2267)	0.97	(19 277)	
Yes		0.03	(348)	0.04	(212)	0.05	(53)	0.02	(25)	0.02	(48)	0.03	(686)	
Follow-up time[b], y	20 032	3.01 (1.19, 5.22)		2.08 (0.86, 4.32)		2.51 (1.10, 4.68)		1.15 (0.62, 1.91)		1.54 (0.79, 2.72)		2.23 (0.94, 4.41)		<.001[c]

Numbers in parentheses after proportions are frequencies. N is the number of nonmissing values.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; DTG, dolutegravir; EVG, elvitegravir; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; IDU, injection drug use; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir.

[a]Pearson χ^2 test.

[b]Median (lower quartile, upper quartile).

[c]Kruskal-Wallis test.

higher proportion of cases among raltegravir initiators (5% or 53 cases; Table 2).

No interactions evaluated were significant; they were therefore removed from final models. Persons initiating INSTI vs NNRTI-based cART had an elevated risk of incident DM (HR, 1.17 [95% CI, .92–1.48]), similar in magnitude to that of PI vs NNRTI initiators (HR, 1.27 [95% CI, 1.07–1.51]), though the CI for INSTIs contained the null (Figure 1). There was essentially no difference in effects comparing INSTI with PI initiators (HR, 0.92 [95% CI, .72–1.18]). The effect among INSTI vs NNRTI initiators was most pronounced, however, among those starting raltegravir (HR, 1.42 [95% CI, 1.06–1.91]) (Figure 1). This contrasted sharply with those initiating elvitegravir- or dolutegravir-based regimens, both of which had essentially null associations with incident DM compared to NNRTI initiators (Figure 1).

In analyses assessing the extent to which 12-month weight changes after cART initiation mediated the cART-class-DM association, there were 17 067 (74%) eligible individuals categorized by initial cART regimen classes (Table 3) and 14 713 (64%) eligible individuals categorized by initial cART regimen core agents (Table 4). Among both groups, there were similar patterns observed regarding younger age, more recent cART initiation, and differential proportions by race and HIV transmission risk category, as seen among persons included in primary analyses (Tables 1 and 2). However, only about 2% of individuals experienced incident DM, though again differences were observed by individual agents: 3% of raltegravir initiators compared to ≤1% among dolutegravir and elvitegravir initiators (Table 4).

In multivariable Cox models evaluating the total and direct (unmediated) effects of initial cART regimen on incident DM among individuals eligible for the mediation analysis, there again was a slight elevation of incident DM risk associated with initiation of an INSTI- compared to an NNRTI-based regimen, although the CI contained the null (HR, 1.08 [95% CI, .75–1.57]). After accounting for 12-month weight change, the effect of initiating an INSTI-based regimen on incident DM was somewhat attenuated (HR, 1.03 [95% CI, .71–1.49]); however, this direct effect estimate was difficult to contrast

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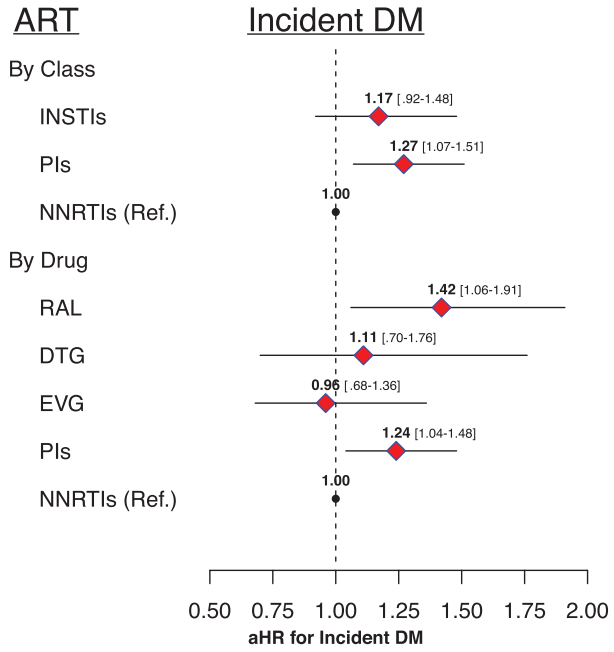

Figure 1. Adjusted hazard ratios (with 95% confidence intervals) for incident diabetes mellitus by initial combination antiretroviral therapy (cART) regimen classes and core agents, among those in participating North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) cohorts initiating cART of ≥45 days' duration between 2007 and 2016. Abbreviations: aHR, adjusted hazard ratio; DM, diabetes mellitus; DTG, dolutegravir; EVG, elvitegravir; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir.

with the total effect or to attribute completely to mediation by weight (Figure 2).

Among those individuals who initiated INSTI-based cART, the total effect of the cART core agent on incident DM was substantial among those initiating raltegravir vs NNRTIs (HR, 1.34 [95% CI, .85–2.09]), and had a slightly attenuated direct effect when accounting for 12-month weight change (HR, 1.26 [95% CI, .80–1.97]) (Figure 2). This was in stark contrast to starting dolutegravir (total effect HR, 0.44 [95% CI, .13–1.46]; direct effect HR, 0.41 [95% CI, .12–1.35]) or elvitegravir (total effect HR, 1.12 [95% CI, .65–1.93]; direct effect HR, 1.08 [95% CI, .63–1.85]) vs NNRTI (Figure 2).

In sensitivity analyses excluding persons who initiated cART regimens that included TAF and including baseline HCV infection and opportunistic infection status, results for the primary and mediation regression analyses were not appreciably different. This was expected, as TAF use was rare in this cohort during the study period (n = 435 or approximately 1.9% of regimens initiated before the end of 2017) and baseline HCV infection and opportunistic infection prevalence were low (≤13% prevalence among all initial cART groups).

Cumulative incidences of incident DM stratified by initial cART regimen or core agent, accounting for all-cause death as a competing risk, revealed similar patterns as those identified in the primary and mediation analyses, though the relative elevation of DM risk due to raltegravir initiation in the primary analysis cohort (Supplementary Figure 1), and after 1-year post–12-month weight measurement in the mediation analysis cohort (Supplementary Figure 2), was more pronounced.

DISCUSSION

In this cohort of PWH from multiple sites across the US and Canada, the rate of incident DM was approximately 10.7 cases per 1000 persons/year over a decade. This is approximately 2-fold higher than the DM incidence in the general US population [24]. Similarly concerning, PWH starting INSTI-based cART had a 17% elevated risk of incident DM compared to those initiating NNRTIs, while those starting PIs had a 27% increased risk, after accounting for several demographic and clinical confounders. However, among INSTIs, those starting raltegravir had more than a 40% elevated risk of incident DM compared to those initiating NNRTIs. When accounting for potential mediation of the relationship between cART exposure and incident DM by 12-month weight change, our analyses revealed attenuation of the total effect of INSTI initiation on incident DM by an absolute amount of 5%. This indicates a residual elevated risk of DM associated with INSTI use of 3% that was unexplained by 12-month weight, though both reduced and increased risks were plausible inferences.

In the modern era, cART-treated PWH now routinely survive for decades and an increasing proportion become overweight or obese with time [1, 6, 11, 25]. Weight gain after cART initiation tends to be greater among persons with lower pretreatment BMI and $CD4^+$ count, and higher HIV-1 RNA [1, 6], which may stem from a reduction in inflammation-related catabolism and basal energy expenditure, or changes in dietary habits or other behaviors (eg, access to smoking cessation treatment), among other factors [18].

Metabolic disease is increasingly common among PWH and the prevention of DM is an area of major clinical importance. The estimated incidence of DM among PWH ranges between 3.1 and 14 cases per 1000 persons/year in prior studies [19,26–29], while the incidence of prediabetes is even higher, with an estimated 125 cases per 1000 persons/year in a recent meta-analysis [30]. Traditional risk factors for DM among PWH are those observed in the general population including older age, increasing BMI and central adiposity, family history of DM, and African American or Hispanic race/ethnicity [10, 30–32]. As observed in the general population, PWH with DM have significantly higher risk of cardiovascular disease, chronic kidney disease, and mortality compared to nondiabetics [7, 9, 10].

While we observed a higher risk of incident DM in NA-ACCORD compared to the general US population, other studies report a lower DM prevalence and incidence among PWH compared to HIV-negative individuals in the same

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Table 3. Characteristics of People Living With Human Immunodeficiency Virus Initiating Antiretroviral Therapy (ART) of ≥45 Days' Duration and With an Available Weight Measure at 12 Months (±6 Months) After ART Initiation Date, 2007–2016, in Participating North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) Cohorts (Those With ≥50 Individuals Receiving Each Core Class), Stratified by Class of Regimen Core

Characteristic	Total No.	NNRTI-Based (n = 8200)		PI-Based (n = 5215)		INSTI-Based (n = 3652)		Combined (N = 17 067)		Interclass *P* Value
Sex assigned at birth	17 067									<.001[a]
Male		0.91	(7455)	0.81	(4229)	0.85	(3120)	0.87	(14 804)	
Female		0.09	(745)	0.19	(986)	0.15	(532)	0.13	(2263)	
Race/ethnicity	16 320									.28[a]
White, non-Hispanic		0.39	(3070)	0.38	(1888)	0.39	(1380)	0.39	(6338)	
Non-white		0.61	(4721)	0.62	(3081)	0.61	(2180)	0.61	(9982)	
HIV transmission risk	17 067									<.001[a]
MSM		0.39	(3220)	0.31	(1598)	0.51	(1852)	0.39	(6670)	
IDU, including MSM/IDU		0.12	(958)	0.14	(748)	0.08	(280)	0.12	(1986)	
Heterosexual		0.14	(1130)	0.19	(997)	0.19	(678)	0.16	(2805)	
Other/unknown		0.35	(2892)	0.36	(1872)	0.23	(842)	0.33	(5606)	
Age, y	17 067	42 (32, 51)		41 (31, 50)		38 (28, 48)		41 (31, 50)		<.001[c]
Baseline weight[b], kg	15 021	78 (69, 89)		76 (67, 87)		77 (67, 89)		77 (68, 89)		<.001[c]
Weight at 1 y after ART[b], kg	17 067	80 (70, 91)		79 (69, 91)		80 (70, 93)		80 (70, 91)		.061[c]
Baseline BMI[b], kg/m^2	14 452	25 (22, 28)		25 (22, 28)		25 (22, 29)		25 (22, 28)		<.001[c]
Baseline CD4$^+$ count[b], cells/μL	15 227	315 (186, 450)		266 (112, 406)		368 (194, 535)		310 (164, 458)		<.001[c]
Baseline $\log_{10}$ HIV-1 RNA[b]	14 525	4.6 (4.0, 5.0)		4.7 (4.1, 5.2)		4.6 (4.1, 5.1)		4.6 (4.1, 5.1)		<.001[c]
Year of ART initiation[b]	17 067	2010 (2008, 2012)		2010 (2009, 2011)		2014 (2012, 2015)		2011 (2009, 2013)		<.001[c]
Incident diabetes mellitus	17 067									<.001[a]
No		0.98	(7999)	0.98	(5116)	0.99	(3605)	0.98	(16 720)	
Yes		0.02	(201)	0.02	(99)	0.01	(47)	0.02	(347)	
Follow-up time[b], y	17 067	2.32 (0.72, 4.47)		1.75 (0.35, 3.32)		1.12 (0.31, 2.29)		1.83 (0.48, 3.64)		<.001[c]

Numbers in parentheses after proportions are frequencies. N is the number of nonmissing values.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; IDU, injection drug use; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Pearson χ^2 test.

[b]Median (lower quartile, upper quartile).

[c]Kruskal-Wallis test.

health system, highlighting the need for further studies of metabolic disease risk factors [9, 11]. An analysis in the Veterans Aging Cohort Study found that the risk of DM accompanying weight gain differed by HIV status; for every 5 pounds of weight gained, the risk of incident DM increased by 14% among PWH compared with 8% among persons without HIV [11]. A disparity in DM incidence following weight gain may relate to differences in the anatomic distribution of the weight, and particularly the propensity for central or visceral abdominal fat accumulation in PWH. The AIDS Clinical Trial Group found that cART-naive PWH randomized to receive tenofovir disoproxil fumarate/emtricitabine plus atazanavir-ritonavir, darunavir-ritonavir, or raltegravir experienced non-uniform gains in fat mass at 96 weeks, averaging 13% for limb fat, 20% for subcutaneous abdominal fat, and 26% for visceral abdominal fat by computed tomographic (CT) imaging [33]. Higher visceral fat gains were accompanied by greater insulin resistance as measured by the homeostatic model assessment [34]. While changes in visceral fat by CT imaging were not significantly different between treatment arms in a substudy, persons starting raltegravir had greater increases in waist circumference at 96 weeks compared to persons who received either of the PIs in the larger parent trial [35]. Furthermore, in the ADVANCE study, cART-naive PWH randomized to dolutegravir-based regimens had greater truncal fat gains compared to those who initiated efavirenz-based regimens, which was particularly apparent among women [3].

While the preferential deposition of central fat on INSTIs may contribute to insulin resistance, recent studies suggest these medications may also adversely affect metabolic health through changes in adipose tissue. In the European Network for AIDS Treatment 022 (NEAT022) study, PWH switched from ritonavir-boosted PI-containing regimens to DTG-containing regimens had 11% lower levels of adiponectin, an insulin sensitizing hormone produced by adipocytes, after 48 weeks, which was disproportionate to the change in weight over the same period [36]. Furthermore, macaques administered INSTIs for 2 weeks to achieve physiologic concentrations similar to cART-treated humans had greater subcutaneous adipose tissue fibrosis and lower adiponectin expression compared to controls, while adipocytes exposed to DTG demonstrated lower adiponectin production [16]. Taken together, these findings suggest INSTI-class medications may contribute to insulin resistance, in part, via adverse effects on adipose tissue, including

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Table 4. Characteristics of People Living With Human Immunodeficiency Virus Initiating Antiretroviral Therapy (ART) of ≥45 Days' Duration and With an Available Weight Measure at 12 Months (±6 Months) After ART Initiation Date, 2007–2016, in Participating North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) Cohorts (Those With ≥50 Individuals Receiving Each Active Agent), Stratified by Active Agent of Regimen Core

Characteristic	Total No.	NNRTI-Based (n = 7559)		PI-Based (n = 3961)		RAL-Based (n = 812)		DTG-Based (n = 758)		EVG-Based (n = 1623)		Combined (N = 14 713)		Interagent *P* Value
Sex assigned at birth	14 713													<.001[a]
Male		0.91	(6911)	0.83	(3276)	0.84	(685)	0.85	(644)	0.88	(1436)	0.88	(12 952)	
Female		0.09	(648)	0.17	(685)	0.16	(127)	0.15	(114)	0.12	(187)	0.12	(1761)	
Race/ethnicity	14 239													.004[a]
White, non-Hispanic		0.40	(2891)	0.38	(1461)	0.45	(353)	0.38	(284)	0.37	(589)	0.39	(5578)	
Non-white		0.60	(4400)	0.62	(2358)	0.55	(438)	0.62	(462)	0.63	(1003)	0.61	(8661)	
HIV transmission risk	14 713													<.001[a]
MSM		0.39	(2921)	0.36	(1432)	0.42	(345)	0.61	(464)	0.61	(992)	0.42	(6154)	
IDU, including MSM/IDU		0.12	(921)	0.16	(635)	0.12	(97)	0.05	(39)	0.07	(114)	0.12	(1806)	
Heterosexual		0.13	(998)	0.21	(830)	0.18	(149)	0.24	(179)	0.19	(311)	0.17	(2467)	
Other/unknown		0.36	(2719)	0.27	(1064)	0.27	(221)	0.10	(76)	0.13	(206)	0.29	(4286)	
Age[b], y	14 713	43 (32, 51)		42 (32, 51)		44 (34, 52)		36 (28, 49)		34 (27, 46)		42 (31, 51)		<.001[c]
Baseline weight[b], kg	13 054	78 (69, 89)		77 (68, 88)		78 (68, 90)		76 (67, 88)		77 (67, 90)		78 (68, 89)		<.001[c]
Weight at 1 y after ART[b], kg	14 713	80 (70, 91)		80 (70, 92)		81 (72, 94)		79 (70, 93)		80 (69, 93)		80 (70, 92)		.093[c]
Baseline BMI[b], kg/m^2	12 635	25 (23, 28)		25 (22, 28)		26 (23, 29)		25 (22, 29)		25 (22, 29)		25 (22, 28)		.022[c]
Baseline CD4$^+$ count[b], cells/μL	12 943	320 (190, 462)		268 (110, 417)		339 (162, 505)		402 (207, 592)		385 (220, 557)		317 (170, 473)		<.001[c]
Baseline $\log_{10}$ HIV-1 RNA[b]	12 286	4.6 (4.0, 5.0)		4.7 (4.1, 5.2)		4.6 (4.0, 5.1)		4.6 (4.1, 5.1)		4.6 (4.1, 5.1)		4.6 (4.0, 5.1)		<.001[c]
Year of ART initiation[b]	14 713	2010 (2008, 2012)		2010 (2008, 2012)		2011 (2010, 2012)		2015 (2015, 2016)		2014 (2014, 2015)		2011 (2009, 2013)		<.001[c]
Incident diabetes mellitus	14 713													<.001[a]
No		0.97	(7364)	0.98	(3875)	0.97	(789)	1.00	(755)	0.99	(1603)	0.98	(14 386)	
Yes		0.03	(195)	0.02	(86)	0.03	(23)	0.00	(3)	0.01	(20)	0.02	(327)	
Follow-up time[b], y	14 713	2.29 (0.71, 4.38)		1.45 (0.24, 3.64)		1.78 (0.54, 3.74)		0.57 (0.16, 1.22)		1.03 (0.30, 2.02)		1.71 (0.42, 3.74)		<.001[c]

Numbers in parentheses after proportions are frequencies. N is the number of nonmissing values.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; DTG, dolutegravir; EVG, elvitegravir; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; IDU, injection drug use; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir.

[a]Pearson χ^2 test.

[b]Median (lower quartile, upper quartile).

[c]Kruskal-Wallis test.

reduced adiponectin production. Notably, a recent study from Uganda reported a 0.47% cumulative incidence of symptomatic hyperglycemia among PWH switched to DTG-based cART compared to 0.03% among PWH receiving non-DTG-based regimens, and in most cases the development of hyperglycemia was not accompanied by weight gain [15]. At present, further studies are needed to determine the role of visceral fat accumulation vs non-weight-related mechanisms in the pathogenesis of metabolic disease among persons starting or switched to INSTIs.

While our study utilized data from a large, multisite cohort broadly representative of PWH in the US [37], the findings may not be generalizable to PWH globally. As is true of many large observational studies using clinical data, we did not have cART adherence or lipodystrophy measures, both of which may be potential mediators; however, our intention-to-treat analytical framework did make use of prescribed cART as a proxy for received cART. Our outcome incorporated HbA1c ≥6.5%, initiation of diabetes-specific medication, or new DM diagnosis along with diabetes-related medication. HbA1c may underestimate fasting blood glucose in PWH, potentially leading to missed diagnoses, while participants diagnosed with DM by fasting blood glucose or oral glucose challenge testing and treated with diet and lifestyle modification, as opposed to medication, may also have been missed [38]. We did not consider exposure to non-HIV medications associated with weight gain, such as hormonal and psychotropic drugs, or tobacco use, or physical activity, though this should only bias our inferences insofar as these factors were differentially distributed by initial cART class. Only 14% of participants were female, and therefore our results may not reflect the burden of treatment-associated DM among PWH worldwide, given greater weight and truncal fat gain observed among women in multiple studies [2, 3, 35]. In addition, we were unable to examine differences in DM by key sex-by-race subgroups in the US and Canada (eg, among black women or Indigenous groups). Finally, we did not assess longitudinal changes in HbA1c or fasting glucose, and did not assess the development of prediabetes, the major risk factor for the development of DM. However, these may be seen as mediators

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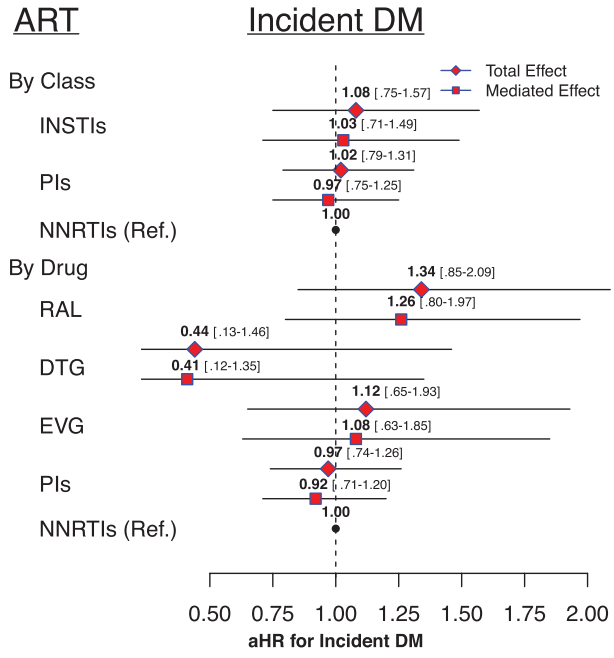

Figure 2. Adjusted hazard ratios (with 95% confidence intervals) for the total effect and the direct (unmediated) effect of initial combination antiretroviral therapy (cART) regimen classes and core agents on incident diabetes mellitus, among those in participating North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) cohorts initiating cART of ≥45 days' duration and with an available weight measure at 12 months (±6 months) after cART initiation date, 2007–2016. Abbreviations: aHR, adjusted hazard ratio; DM, diabetes mellitus; DTG, dolutegravir; EVG, elvitegravir; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir.

on causal pathways including intermediate weight gain, which we did account for in our analyses.

In summary, weight gain and the metabolic health of PWH initiating cART should be monitored by clinicians, and the use of PI or INSTI- vs NNRTI-based cART regimens, particularly those containing raltegravir, may confer greater risk of incident DM. Indeed, in our analyses, raltegravir was the lone INSTI for which a strong and significant association with incident DM was observed. It is a strength of this study that we were able to quantify both adjusted and mediated relationships between initial cART class and subsequent DM using rigorous analytic methods in a well-characterized cohort with rich longitudinal clinical data. However, further research will be required to identify patients at highest risk of metabolic complications, the mechanisms driving the observed risk differences, and appropriate risk-reducing interventions in an aging and increasingly overweight population of PWH.

Supplementary Data

Supplementary materials are available at *Clinical 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

Disclaimer. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of Gilead or the National Institutes of Health (NIH).

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