Impact of change in body mass index on the risk of hypertension and dyslipidemia in people receiving integrase inhibitors and/or tenofovir alafenamide compared to other contemporary antiretroviral regimens in RESPOND

Running Header: BMI changes and incident hypertension and dyslipidemia in PLWH

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ABSTRACT

Objective: To assess whether changes in body mass index (BMI) differentially increase hypertension or dyslipidemia risk in people with HIV (PLWH) receiving integrase inhibitors (INSTI) and/or tenofovir alafenamide (TAF) versus other regimens.

Methods: PLWH ≥18 years, receiving INSTIs or contemporary non-INSTIs, with baseline and ≥2 follow-up BMI and lipid/blood pressure measurements, were followed from baseline until the earliest event or last visit or 31/12/2021. We used multivariable Poisson regression adjusted for time-updated BMI to determine unadjusted and adjusted incidence rate ratios (IRR) of hypertension and dyslipidemia in PLWH receiving INSTIs and/or TAF and test for interaction between time-updated ART and BMI.

Results: 9941 and 5484 PLWH were included in hypertension and dyslipidemia analyses, respectively. In the univariable model, hypertension was more common in PLWH receiving INSTI with TAF (IRR 1.70, confidence intervals 1.54-1.88) or INSTI without TAF (1.41,1.30-1.53), compared to those receiving neither INSTI nor TAF. Adjustment for time-updated BMI and confounders attenuated risk in PLWH receiving INSTI with (1.48, 1.31-1.68) or without TAF (1.25, 1.13-1.39). Similarly, dyslipidemia was more common in PLWH using TAF with INSTI (1.24, 1.10-1.40) and TAF alone (1.22, 1.03-1.44). Adjustment for BMI and confounders attenuated the risk in PLWH receiving TAF with INSTI (1.21, 1.07-1.37), while the risk in those receiving TAF alone (1.15, 0.96-1.38) became non-significant. Hypertension and dyslipidemia increased equally with increasing BMI between regimens (*P*-interaction=0.459 and 0.303, respectively).

Conclusion: In RESPOND, INSTI use was associated with incident hypertension and TAF with dyslipidemia. The relationship between BMI and hypertension or dyslipidemia did not differ between ART regimens.

Abstract word count: 250, word limit 250

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INTRODUCTION

By June 2021, approximately 22 million people living with HIV (PLWH) were receiving integrase inhibitor (INSTI)-based regimens worldwide[1]. However, there are increasing concerns about the metabolic safety of INSTIs because of their association with weight gain[2,3]. The extent and severity of INSTI-associated weight gain varies for individual antiretroviral drugs within the class, with a higher risk associated with dolutegravir (DTG), bictegravir (BIC), and raltegravir (RAL) than with elvitegravir (EVG) [3–5]. In addition, tenofovir alafenamide (TAF), which is increasingly preferred over tenofovir disoproxil fumarate (TDF), is also associated with weight gain, particularly when used concurrently with INSTIs[3,6].

Similar to the general population, weight gain in PLWH is associated with hypertension[7], diabetes mellitus[8], dyslipidemia[9], and obesity with cardiovascular disease[10]. Analyses in smaller cohorts have reported increases in blood pressure (BP) or incident hypertension following the initiation of INSTIs[9,11–15]. The evidence linking INSTI use to dyslipidemia is inconsistent, with some studies reporting a lower risk[16,17] and others reporting weight-related increases in lipid levels[18,19]. In contrast, the evidence linking TAF use to increases in lipid levels is stronger[17,20].

It remains unclear whether PLWH receiving INSTIs and/or TAF are at an increased risk of weight-associated clinical events or whether INSTI and/or TAF-associated weight gain differentially increases the risk of clinical events compared to weight gain from other causes. Therefore, we compared the risk of new-onset hypertension or dyslipidemia in PLWH receiving INSTIs and/or TAF versus regimens without INSTI and TAF and determined whether increases in BMI could explain any associations between ART regimens and hypertension or dyslipidemia.

METHODS

Study design

The study was conducted within RESPOND, a consortium of 19 observational cohorts with 36,000 PLWH in Europe and Australia. The details of cohort membership and data collection procedures

have been reported previously[17,21]. Briefly, cohorts collect data on demographics, ART, CD4 and HIV RNA, laboratory results, including serum lipids, BP, and clinical events, and transmit the data to a central coordinating center annually via the HIV cohort data exchange protocol (HICDEP) (https://hicdep.org/). All data are checked for completeness and accuracy. Overall, 13 cohorts with sufficient data on BP and lipids were included in this analysis.

Study participants

Eligible participants were ≥ 18 years and received ART consisting of nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and an INSTI (RAL, DTG, BIC, or EVG) or boosted protease inhibitors (PI/b) (darunavir [DRV/b] and atazanavir [ATV/b]) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) (efavirenz [EFV], rilpivirine [RPV]). The baseline date was the latest of 01/01/2012, cohort entry date or ART initiation date, whichever occurred later. Participants were included if they had no hypertension or dyslipidemia at baseline and had available BMI at baseline with at least two subsequent BMIs (≥12 months apart) and lipid or BP measurements. We excluded participants without baseline CD4 or HIV RNA results and those receiving non-ART medications associated with weight changes[22]., including antipsychotics and mood stabilizers, corticosteroids, insulin, and insulin secretagogues.

Study outcomes

The primary outcomes of this analysis were incidence rate ratios (IRRs) of hypertension and dyslipidemia, assessed separately. Consistent with prior RESPOND analyses[23,24], hypertension was considered to have occurred on the earliest date of the following events: two consecutive measurements of systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg; a single SBP measurement ≥140 mmHg and/or DBP measurement ≥90 mmHg with the use of antihypertensive drugs within 6 months; or the initiation of antihypertensive drugs without a recorded high BP. Dyslipidemia was defined as total cholesterol (TCHOL) greater than 240 mg/dL and/or high-density lipoprotein cholesterol (HDL) <35 mg/dL, and/or triglycerides greater than 200 mg/dL, and/or the initiation of statins or fibrates[17].

Confounders and Effect Modifiers

The primary exposure was time-updated ART regimens (INSTI with TAF, INSTI without TAF, or TAF without INSTI) versus regimens without INSTIs or TAF. Other covariates (prespecified *a priori)* included in the multivariable model were: time-updated BMI, baseline lipid and BP values, age, ethnicity, sex, baseline calendar year, smoking status (current, previous, never smoked, or unknown), diabetes mellitus (commencement of hypoglycemic treatment and/or blood glucose level ≥ 11.1mmol/L and/or HbA1c ≥6.5% and/or reported diagnosis), prior AIDS, cardiovascular disease (stroke and/or acute myocardial infarction and/or invasive coronary procedures), estimated glomerular filtration rate (eGFR), HIV RNA, nadir CD4 and baseline CD4 counts, and duration since HIV diagnosis, and cumulative exposure to antiretrovirals that were not of primary interest, but have been associated with hypertension (nevirapine, stavudine, protease inhibitors [PIs]) or dyslipidemia (abacavir, PIs)[23,25–28]. The covariates closest to baseline, but within one year before and up to seven days after, were considered baseline. Furthermore, hepatitis C infection was defined as a positive antibody test, positive RNA and/or genotype test or the initiation of anti-HCV medications. Hepatitis B virus was defined as a positive surface antigen and/or positive DNA test. Finally, chronic kidney disease was defined as two successive eGFR ≤60 ml/min/1.73m2 [without race adjustment] at least 90 days apart.

Statistical analysis

We summarized the baseline characteristics of participants who developed hypertension and dyslipidemia (separately) and those who did not. Follow-up began from baseline and was censored at the earliest date of an event, the last visit date, or 31/12/2021. Multivariable Poisson regression was used to determine the IRRs of hypertension and dyslipidemia in PLWH receiving INSTI and/or TAF versus regimens without INSTI or TAF. Switches between different ART classes were considered regimen changes, whereas within-class substitutions were not. Furthermore, since TDF and EFV may be weight suppressive[2,29,30], only the period after the first six months of these drugs was included. Finally, we performed individual comparisons for antiretroviral drugs with >100 events.

First, we fitted a univariable for time-updated ART regimens and then a multivariable model adjusted for all covariates (except time-updated BMI). Finally, we included time-updated BMI in the

multivariable model to determine the impact of BMI changes on hypertension and dyslipidemia risk. Comparison of the relationship between BMI and incident hypertension and dyslipidemia involved testing for interaction between time-updated BMI and ART regimens. The null hypothesis was that there was no interaction between time-updated BMI and the current ART regimen. Rejection of the null hypothesis suggests a statistically different change in the risk of hypertension and dyslipidemia due to BMI changes in PLWH receiving different ART combinations. In addition, we assessed the interaction between sex and time-updated ART regimens. Finally, we present forest plots of event rates for each ART regimen by time-updated BMI split into quintiles. All statistical tests were two-sided, and statistical significance was set at $P<0.05$.

Sensitivity Analyses

We performed several sensitivity analyses. First, we hypothesized that past values might better capture dynamic weight changes and fitted BMI lagged by 12 months. Second, we disregarded the six-month washout and censored follow-up upon switching from or to TDF/EFV. Third, we defined BMI increase as ≥7% increase from the baseline value[3]. Fourth, since EVG has not been associated with weight gain like other INSTIs[3], we performed an analysis in which EVG was excluded from the INSTIs class. Fifth, to minimize confounding due to prior exposure to ABC, PIs, and ART, we performed separate analyses in which participants with prior exposure to ART or these agents were excluded. Finally, we considered a dyslipidemia definition without hypertriglyceridemia.

RESULTS

Participant inclusion in the hypertension analysis

Of the 28941 PLWH who were receiving eligible ART regimens, 13946 (48.2%) participants had baseline BMI and BP results and ≥2 follow-up measurements, 3652 (27.3%) of whom had hypertension and were excluded (Figure S1). Among the 9704 eligible participants, the median DBP and SBP (interquartile range, IQR) were 78 (70-82) and 121 (114-130) mmHg, respectively; the median age was 44 (36-51) years, 7327 (75.5 %) were male, and 824 (8.5%) were black (Table 1). During follow-up, 6086 (62.7%) participants received INSTIs, 2988 (49.1%) of whom received TAF

simultaneously. Participants who received INSTIs were similar to those who received non-INSTIs (Table S1).

Table 1: Baseline characteristics of participants with versus those without incident hypertension

Variable	Categories†	No incident hypertension (n=6727)		Incident Hypertension (n=2,977)		Total (n=9,704)	
		n	%	n	%	n	%
Gender	Female	1,771	26.3	606	20.4	2,377	24.5
	Male	4,956	73.7	2,371	79.6	7,327	75.5
Ethnicity‡‡	White	4,673	69.5	2,280	76.6	6,953	71.7
	Black	548	8.2	276	9.3	824	8.5
	Other/Unknown	1,506	22.4	421	14.1	1,927	19.9
Region	W. Europe	3,313	49.3	1,890	63.5	5,203	53.6
	S. Europe	700	10.4	140	4.7	840	8.7
	N. Europe*	2,714	40.3	947	31.8	3,661	37.7
Route of HIV acquisition	MSM	3,240	48.2	1,511	50.8	4,751	49.0
	IDU	894	13.3	326	11.0	1,220	12.6
	Heterosexual	2,243	33.3	987	33.2	3,230	33.3
	Other/Unknown	350	5.2	153	5.1	503	5.2
ART Status	Naive	1,511	22.5	677	22.7	2,188	22.6
	Experienced	5,216	77.5	2,300	77.3	7,516	77.5
Prior AIDS	Yes	1,284	19.1	687	23.1	1,971	20.3
	No	5,443	80.9	2,290	76.9	7,733	79.7
Hepatitis B infection	Positive	357	5.3	147	4.9	504	5.2
	Negative	5,796	86.2	2,578	86.6	8,374	86.3
	Unknown	574	8.5	252	8.5	826	8.5
Hepatitis C infection	Positive	1,453	21.6	551	18.5	2,004	20.7
	Negative	4,272	63.5	1,943	65.3	6,215	64.1
	Unknown	1,002	14.9	483	16.2	1,485	15.3
Smoking Status	Current	2,266	33.7	1,009	33.9	3,275	33.8
	Previous	822	12.2	394	13.2	1,216	12.5
	Never	2,422	36.0	1,054	35.4	3,476	35.8
	Unknown	1,217	18.1	520	17.5	1,737	17.9
Chronic Kidney Disease	Yes	411	6.1	361	12.1	772	8.0
	No	6,287	93.5	2,612	87.7	8,899	91.7
	Unknown	29	0.4	4	0.1	33	0.3
Diabetes Mellitus	Yes	181	2.7	164	5.5	345	3.6
	No	6,203	92.2	2,729	91.7	8,932	92.0
	Unknown	343	5.1	84	2.8	427	4.4
Cardiovascular disease	Yes	27	0.4	23	0.8	50	0.5
	No	6033	89.7	2,837	95.3	8870	91.4
	Unknown	667	9.9	117	3.9	784	8.1
Lipid-lowering therapy	Yes	189	2.8	144	4.8	333	3.4
	No	6538	97.2	2,833	95.2	9371	96.6
		Median (IQR)	**# missing (%)**	**Median (IQR)**	**# missing (%)**	**Median (IQR)**	**# missing (%)**
Age (years)		43(35,50)	0(0)	47(39,54)	0(0)	44(36,51)	0(0)
Baseline CD4 (cells/μL)		548(368,744)	0(0)	535(364,723)	0(0)	544(367,739)	0(0)
Nadir CD4 (cells/μL)		254(132,391)	0(0)	228(110,356)	0(0)	246(125,379)	0(0)
Baseline HIV RNA (copies/mL)		39(19,408)	0(0)	39(19,268)	0(0)	39(19,367)	0(0)
Baseline BMI (kg/m2)		23.1(21.0,25.4)	0(0)	24.2(21.9,26.9)	0(0)	23.4(21.2,25.9)	0(0)
Baseline HDL (mg/dL)		47(38,58)	876(13.0)	46(37,58)	274(9.2)	46(38,58)	1150(11.9)
Baseline TCHOL (mg/dL)		182(155,211)	453(6.7)	187(159,217)	190(6.4)	183(155,213)	643(6.6)
Baseline TRIG (mg/dL)		115(80,167)	597(8.9)	126(89,186)	215(7.2)	117(82,174)	812(8.4)
Baseline LDL (mg/dL)		105(85,131)	4346(64.6)	109(86,133)	1664(55.9)	106(85,132)	6010(61.9)
Baseline GFR ml/min/1.73 m2		102(87,113)	488(7.3)	98(84,109)	228(7.7)	101(86,112)	716(7.4)
Baseline DBP (mmHg)		75(70,80)	0(0)	80(75,86)	0(0)	78(70,82)	0(0)
Baseline SBP (mmHg)		120(110,129)	0(0)	129(120,136)	0(0)	121(114,130)	0(0)
ART duration (years) **		9.5(4.6,15.1)	1511(22.5)	10.6(5.6,16.4)	677(22.7)	9.8(4.9,15.6)	2188(22.6)
5-year predicted CVD risk (%)		1.8(0.8,3.5)	911(13.5)	2.8(1.5,5.2)	298(10.0)	2.1(1.0,4.0)	1209(12.5)
Number of follow-up BP measures		8(4,12)	0(0)	13(8,18)	0(0)	9(5,1)	0(0)
Baseline date (mm-yy)		11/15(01/12,04/16)	0(0)	04/14(01/12,11/15)	0(0)	09/14(01/12,03/16)	0(0)
Cumulative exposure to antiretroviral agents (years)**		**median (IQR)**	**# exposed (%)**	**Median (IQR)**	**# exposed (%)**	**Median (IQR)**	**# exposed (%)**
Cumulative exposure to NRTIs		9.3(4.6,14.7)	5187(77.1)	10.3(5.4,15.9)	2292(77.0)	9.6(4.8,15.1)	7479(77.1)
Cumulative exposure to NNRTIs		5.8(2.0,10.6)	3375(50.2)	6.5(2.2,11.3)	1481(49.8)	6.0(2.1,10.8)	4856(50.0)
Cumulative exposure to PIs		6.4(2.6,11.6)	3665(54.5)	6.5(2.7,11.8)	1771(59.5)	6.5(2.6,11.7)	5436(56.0)
Cumulative exposure INSTIs		3.0(1.5,4.8)	299(4.4)	2.7(0.7,4.8)	89(3.0)	3.0(1.4,4.8)	388(4.0)
Cumulative exposure to abacavir		4.6(1.7,8.7)	1877(27.9)	5.3(1.9,9.4)	917(30.8)	4.8(1.7,9.0)	2794(28.8)
Cumulative exposure to stavudine		3.2(1.5,5.3)	1195(17.8)	3.4(1.5,5.5)	669(22.5)	3.3(1.5,5.4)	1864(19.2)
Cumulative exposure to nevirapine		1.7(0.3,6.2)	850(12.6)	1.8(0.3,5.4)	416(14.0)	1.8(0.3,6.0)	1266(13.1)
Cumulative exposure to efavirenz		5.8(1.8,10.7)	2665(39.6)	6.9(2.1,11.3)	1182(39.7)	6.1(1.9,10.8)	3847(39.6)
Cumulative exposure to zidovudine		5.4(2.1,8.7)	1654(24.6)	5.5(2.3,8.6)	765(25.7)	5.4(2.1,8.6)	2419(24.9)
Cumulative exposure to darunavir		3.4(1.4,5.7)	1395(20.7)	3.7(1.3,6.0)	654(22.0)	3.4(1.4,5.8)	2049(21.1)
Cumulative exposure to indinavir		1.8(0.7,3.7)	731(10.9)	1.9(0.7,3.6)	434(14.6)	1.8(0.7,3.6)	1165(12.0)
Cumulative exposure to lopinavir		2.8(0.9,6.2)	1505(22.4)	2.7(1.0,5.8)	691(23.2)	2.8(0.9,6.1)	2196(22.6)
Cumulative exposure to TDF‖		6.1(3.1,9.3)	4168(61.96)	6.4(3.3,9.5)	1845(61.98)	6.2(3.1,9.4)	6013(61.96)

Caption for Table 1

1. NSTI-integrase inhibitors, PI-protease inhibitors, NRTI-nucleosi(t)ide reverse transcriptase inhibitors, NNRTI-non-nucleoside reverse transcriptase inhibitors; CVD-cardiovascular disease, eGFR-estimated glomerular filtration rate (GFR), using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, HDL-high-density lipoprotein, LDL-low-density lipoprotein (LDL), TCHOL-total cholesterol, TRIG-triglycerides, IDU-intravenous drug use, MSM-men who have sex with men, SBP-systolic blood pressure, DBP-diastolic blood pressure, ART-antiretroviral therapy.
2. All lipids are expressed in mg/dL. To convert triglyceride levels from mg/dL to mmol/L, divide by 88.57. For HDL, LDL, and total cholesterol, divide by 38.67.
3. Note *including Australia.
4. ⁑A few cohorts are prohibited (by their jurisdictions) from reporting ethnicity. Two participants from Eastern Europe were added to Northern Europe for analysis.
5. **The stated ART duration and cumulative exposure period is for participants receiving ART before baseline. Exposure to TAF at baseline is not shown because TAF was approved in Europe in 2017 (after the baseline date).
6. †Other categories (other than those stated), including unknown status.
7. ⁑TDF-tenofovir disoproxil fumarate

Participant inclusion in the dyslipidemia analysis

Of the 28941 PLWH receiving contemporary ART regimens, 12391 (49.2%) had baseline BMI and lipid measures and ≥ two follow-up measurements, 7160 (57.8%) of whom had dyslipidemia at baseline and were excluded (Figure S2). In the 5231 eligible participants, the median baseline age was 43 (35-50) years, while the median (IQR) baseline HDL, TCHOL, triglycerides, and LDL-low-density cholesterol (LDL) levels were 52 (43-62), 177 (154,199), 94 (71-128), and 101 (84-122) mg/dL, respectively. The majority (75.7%) were male, and 583 (11.2%) were black (Table 2). During follow-up, 2716 (52.9%) received INSTIs, 1242 (45.7%) of whom received TAF concurrently. Participants who received INSTI were largely similar to those who consistently received non-INSTIs (Table S2).

Table 2: Baseline characteristics of participants with incident dyslipidemia versus those without

Variable	Categories†	No incident dyslipidemia (N=2,542)		Incident dyslipidemia (n=2,689)		Total (n=5,231)	
		n	%	n	%	n	%
Gender	Female	807	31.8	628	23.4	1,435	27.4
	Male	1,735	68.3	2,061	76.7	3,796	72.6
Ethnicity‖	White	1,718	67.6	1,984	73.8	3,702	70.8
	Black	349	13.7	234	8.7	583	11.2
	Other/Unknown	475	18.7	471	17.5	946	18.1
Region	W. Europe	1,253	49.3	1,464	54.4	2,717	51.9
	S. Europe	307	12.1	285	10.6	592	11.3
	N. Europe*	982	38.6	940	35.0	1,922	36.7
Route of HIV acquisition	MSM	1,121	44.1	1,359	50.5	2,480	47.4
	IDU	328	12.9	313	11.6	641	12.3
	Heterosexual	951	37.4	892	33.2	1,843	35.2
	Other/Unknown	142	5.6	125	4.7	267	5.1
ART Status	Naive	643	25.3	686	25.5	1,329	25.4
	Experienced	1,899	74.7	2,003	74.5	3,902	74.6
Prior AIDS	Yes	449	17.7	533	19.8	982	18.8
	No	2,093	82.3	2,156	80.2	4,249	81.2
Hepatitis B infection	Positive	148	5.8	140	5.2	288	5.5
	Negative	2,176	85.6	2,269	84.4	4,445	85
	Unknown	218	8.6	280	10.4	498	9.5
Hepatitis C infection	Positive	1,708	67.2	1,798	66.9	3,506	67.0
	Negative	507	19.9	530	19.7	1,037	19.8
	Unknown	327	12.9	361	13.4	688	13.2
Smoking Status	Current	753	29.6	853	31.7	1,606	30.7
	Previous	283	11.1	312	11.6	595	11.4
	Never	1,013	39.9	992	36.9	2,005	38.3
	Unknown	493	19.4	532	19.8	1,025	19.6
Chronic Kidney Disease	Yes	139	5.5	200	7.4	339	6.5
	No	2,398	94.3	2,483	92.3	4,881	93.3
	Unknown	5	0.2	6	0.2	11	0.2
Diabetes Mellitus	Yes	59	2.3	80	3.0	139	2.7
	No	2,375	93.4	2,505	93.2	4,880	93.3
	Unknown	108	4.3	104	3.9	212	4.1
Cardiovascular disease	Yes	10	0.4	6	0.2	16	0.3
	No	2,260	88.9	2,429	90.3	4,689	89.6
	Unknown	272	10.7	254	9.5	526	10.1
		Median (IQR)	**# missing (%)**	**Median (IQR)**	**# missing (%)**	**Median (IQR)**	**# missing (%)**
Age (years)		42(34,50)	0(0)	44(35,51)	0(0)	43(35,50)	0(0)
Baseline CD4 (cells/µL)		521(360,704)	0(0)	520(350,711)	0(0)	520(356,709)	0(0)
Nadir CD4 (cells/µL)		259(145,398)	0(0)	258(138,391)	0(0)	258(140,393)	0(0)
Baseline HIV RNA (copies/mL)		39.0(19,499)	0(0)	39(19,499)	0(0)	39(19,499)	0(0)
Baseline BMI (kg/m2)		22.9(20.9,25.3)	0(0)	23.6(21.4,26.3)	0(0)	23.3(21.1,25.8)	0(0)
Baseline HDL (mg/dL)		55(46,66)	277(10.9)	49(41,58)	211(7.9)	52(43,62)	488(9.3)
Baseline TCHOL (mg/dL)		170(151,191)	9(0.4)	182(159,206)	17(0.6)	177(155,199)	26(0.5)
Baseline TRIG (mg/dL)		82(62,109)	109(4.3)	106(80,144)	75(2.8)	94(71,127)	184(3.5)
Baseline LDL (mg/dL)		96(80,116)	1449(57)	108(89,128)	1584(58.9)	101(84,122)	3033(58.0)
Baseline GFR ml/min/1.73 m2		103(91,115)	157(6.18)	102(87,113)	211(7.9)	103(89,114)	368(7.0)
Baseline DBP (mmHg)		79(70,85)	131(5.15)	80(70,85)	154(5.73)	80(70,85)	285(5.5)
Baseline SBP (mmHg)		122(114,134)	131(5.15)	125(116,136)	154(5.73)	124(115,135)	285(5.5)
ART duration (years)**		9.7(4.8,15.1)	643(25.3)	9.4(4.8,15.0)	686(25.51)	9.6(4.8,15.0)	1329(25.4)
5-year predicted CVD risk (%)		1.4(0.6,2.8)	374(14.71)	1.9(0.9,3.5)	344(12.79)	1.7(0.8,3.2)	718(13.7)
Number of follow-up lipid tests		8(4,13)	0(0)	11(7,17)	0(0)	10(5,15)	0(0)
Baseline date (mm/yy)		11/14(01/12,06/16)	0(0)	08/13(01/12,11/15)	0(0)	05/14(01/12,03/16)	0(0)
Cumulative exposure to antiretroviral agents (years)**		**Median (IQR)**	**# exposed (%)**	**Median (IQR)**	**# exposed (%)**	**Median (IQR)**	**# exposed (%)**
Cumulative exposure to NRTIs		9.6(4.7,14.9)	1895(74.6)	9.2(4.7,14.6)	1997(74.4)	9.4(4.7,14.8)	3892(74.4)
Cumulative exposure to NNRTIs		6.5(2.4,11.5)	1301(51.2)	6.3(2.5,10.9)	1355(50.4)	6.4(2.4,11.2)	2656(50.8)
Cumulative exposure to PIs		5.9(2.3,10.7)	1256(49.4)	6.1(2.5,10.8)	1323(49.2)	6.0(2.4,10.7)	2579(49.3)
Cumulative exposure to INSTIs		3.0(1.9,4.4)	127(5.0)	3.1(1.7,4.6)	126(4.7)	3.1(1.8,4.5)	253(4.8)
Cumulative exposure to abacavir		4.4(1.6,9.1)	640(25.2)	4.5(1.8,8.8)	649(24.1)	4.5(1.7,9.0)	1289(24.6)
Cumulative exposure to stavudine		2.7(1.0,5.2)	391(15.4)	3.5(1.5,5.6)	422(15.7)	3.2(1.2,5.4)	813(15.5)
Cumulative exposure to nevirapine		1.1(0.2,4.6)	259(10.2)	2.0(0.3,6.0)	302(11.2)	1.5(0.2,5.3)	561(10.72)
Cumulative exposure to efavirenz		7.1(2.5,11.8)	1094(43.0)	6.4(2.6,11.1)	1129(42.0)	6.7(2.6,11.4)	2223(42.5)
Cumulative exposure to zidovudine		5.3(1.8,8.9)	578(22.7)	5.7(2.8,8.6)	633(23.5)	5.5(2.3,8.8)	1211(23.2)
Cumulative exposure to darunavir		3.2(1.3,5.4)	444(17.5)	3.2(1.4,6.1)	468(17.4)	3.2(1.3,5.8)	912(17.4)
Cumulative exposure to indinavir		2.0(0.8,3.5)	259(10.2)	1.9(0.8,4.2)	282(10.5)	2.0(0.8,3.9)	541(10.3)
Cumulative exposure to lopinavir		2.3(0.7,5.3)	467(18.4)	2.1(0.7,4.9)	450(16.7)	2.2(0.7,5.1)	917(17.5)

Caption for Table 2

1. INSTI-integrase inhibitors, PI-protease inhibitors, NRTI-nucleosi(t)ide reverse transcriptase inhibitors, NNRTI-non-nucleoside reverse transcriptase inhibitors; CVD-cardiovascular disease, eGFR-estimated glomerular filtration rate (GFR), using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, HDL-high-density lipoprotein, LDL-low-density lipoprotein (LDL), TCHOL-total cholesterol,

TRIG-triglycerides, IDU-intravenous drug use, MSM-men who have sex with men, SBP-systolic blood pressure, DBP-diastolic blood pressure, ART-antiretroviral therapy.

2. All lipids are expressed in mg/dL. To convert triglyceride levels from mg/dL to mmol/L, divide by 88.57. For HDL, LDL, and total cholesterol, divide by 38.67.
3. Note *including Australia.
4. ‖A few cohorts are prohibited (by their jurisdictions) from reporting ethnicity. 15 participants were in Eastern Europe but were added to Northern Europe for analysis.
5. **The stated ART duration and cumulative exposure period is for participants receiving ART before baseline. Exposure to TAF at baseline is not shown because TAF was approved in Europe in 2017 (after the baseline date).
6. †Other categories (other than those stated), including unknown status.

Incidence of hypertension

Of the 9704 participants without hypertension, 2977 (30.7%) developed hypertension during 39993 person-years (incidence rate [IR]: 74 [95% confidence interval, CI 72-77] per 1000 person-years). Participants who developed hypertension were more likely to be older, male, have diabetes mellitus, CKD, have higher baseline SBP, DBP, and lipid levels, and be on lipid-lowering therapy (Table 1). The incidence of hypertension was higher in PLWH receiving INSTIs with TAF (102, CI 94-111) and those without TAF (I84, CI 79-90) or TAF without INSTIs (73, CI 64-84) than in those receiving regimens without TAF or INSTIs (60, CI 57–64) (Figure 1).

Incidence of dyslipidemia

In the dyslipidemia analysis, 5231 without dyslipidemia at baseline were followed-up over 19547 person-years, and 2689 (51.4%) developed dyslipidemia (IR: 138 [133-143] per 1000 person-years). Participants with incident dyslipidemia were older, more likely to be male, current smokers, and had higher baseline lipid levels (Table 2). The incidence rates were higher in participants concurrently receiving TAF with INSTI (161, CI 146-177) and in those receiving TAF without INSTIs (157, CI 136-181) than in those receiving INSTI without TAF (139, CI 129-149) or ART regimens without TAF or INSTIs (129, CI 122-136) (Figure 1).

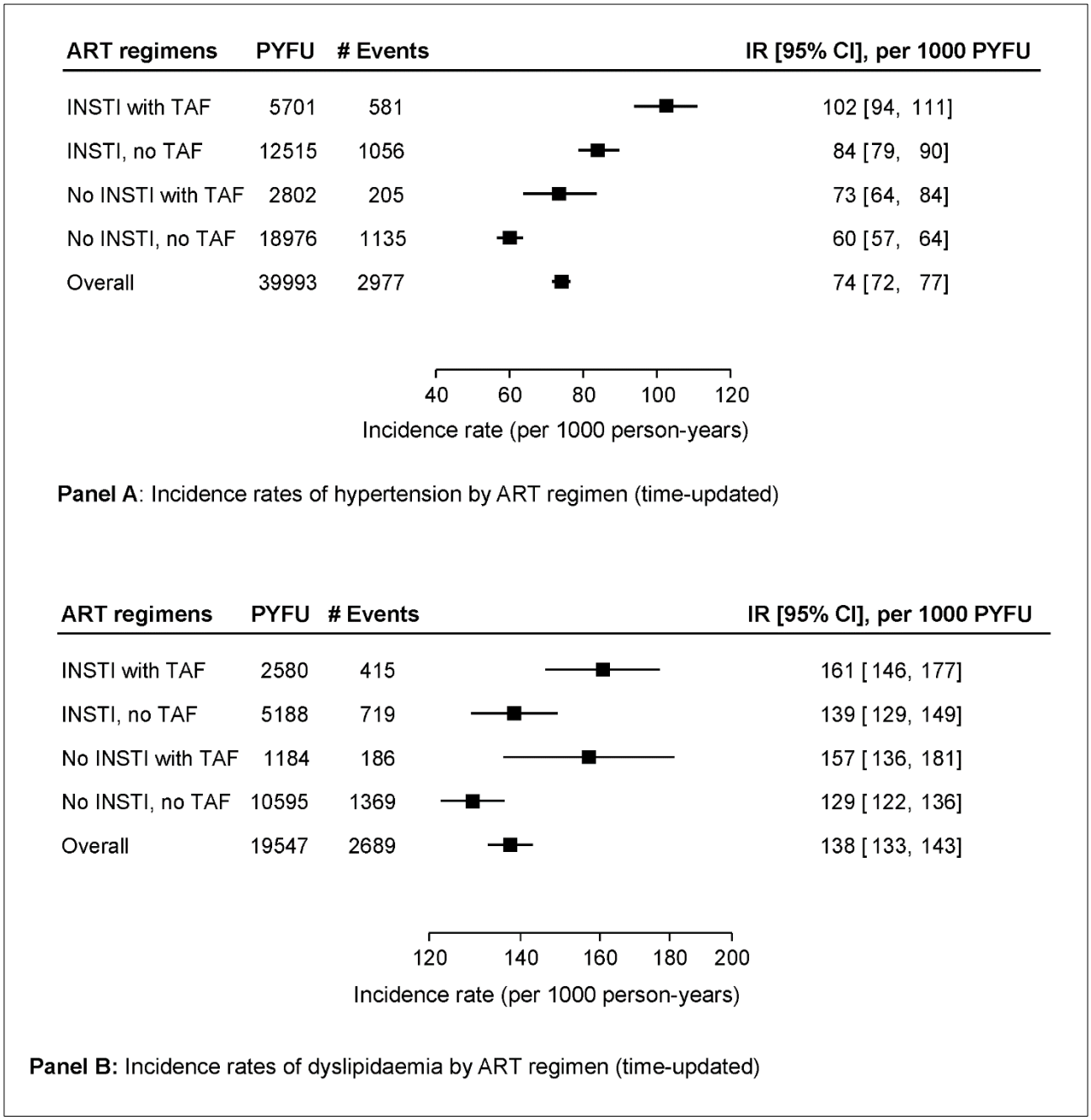


Figure 1: Unadjusted incidence rates of hypertension (panel A) and dyslipidemia (panel B) in PLWH currently receiving (i.e., time-updated) combinations of INSTI and TAF versus regimens without INSTI or TAF

Caption for Figure 1

1. TAF-tenofovir alafenamide, INSTI-integrase strand transfer inhibitors, ART-antiretroviral therapy, IR-incidence rates (per 1000 person-years).
2. "INSTI with TAF" means regimen containing TAF and an INSTI, "INSTI, no TAF" means regimen containing INSTI but without TAF, "No INSTI, TAF" means regimen containing TAF but without INSTI "No INSTI/ TAF" means regimen containing without INSTI or TAF.
3. The multivariable model was adjusted for baseline lipid and BP values, age, ethnicity, sex, baseline calendar year, smoking status, baseline BMI, baseline diabetes mellitus status, prior AIDS, CVD, estimated glomerular filtration rate (eGFR), HIV RNA, CD4 nadir, baseline CD4 counts, duration

since HIV diagnosis, and cumulative exposure to potentially confounding ARVs (abacavir, nevirapine, stavudine, indinavir, and lopinavir). All covariates were prespecified *a priori*:

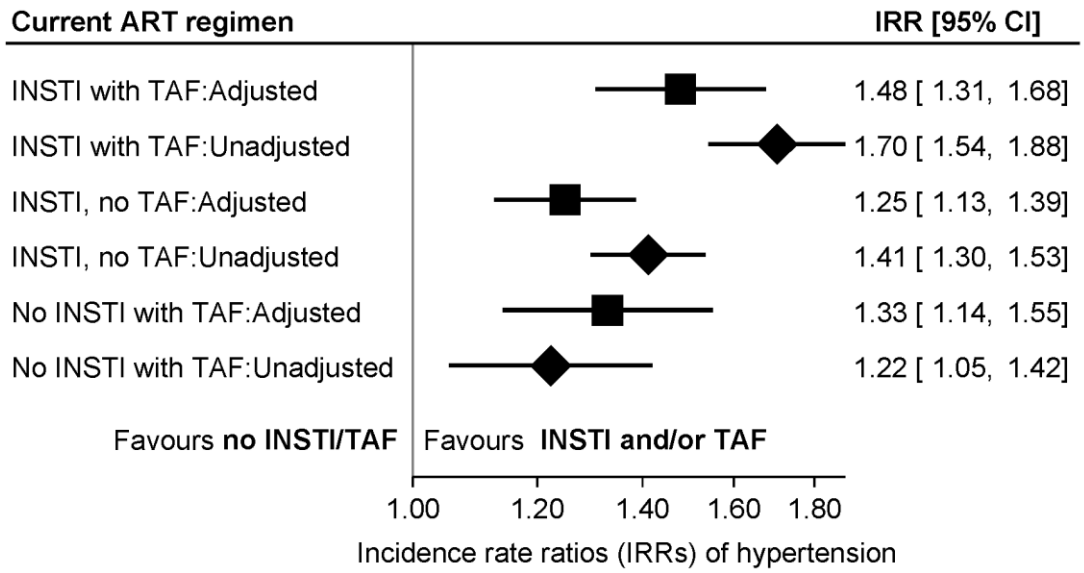
Incidence rate ratios of hypertension in PLWH receiving combinations of INSTI and TAF versus those not receiving INSTI or TAF

In the univariable model, hypertension was more common in PLWH receiving INSTI with TAF (IRR 1.70, CI 1.54-1.88) or without TAF (1.41, CI 1.30-1.53) than those receiving neither INSTI nor TAF. In the multivariable model that adjusted for all confounders but not time-updated BMI, the risk of hypertension was attenuated but remained higher in PLWH receiving INSTI with TAF (adjusted incidence rate ratio (aIRR) 1.56, CI 1.38-1.77) or without TAF (1.29, CI 1.16-1.42), compared to regimens without INSTI or TAF. When time-updated BMI was added to the model, the risk was further attenuated but remained higher in PLWH receiving INSTI with TAF (1.48, CI 1.31-1.68) or without TAF (1.25, CI 1.13-1.39) (Figure 2). The risk of hypertension was consistently higher in PLWH receiving INSTI with TAF across all BMI quintiles (Figure S3). The association between ART regimens and hypertension was not different by sex (*P*-interaction=0.119). Overall, the risk of hypertension increased with increasing time-updated BMI, and the association was not different in PLWH receiving different ART combinations (*P*-interaction=0.459) (Table S5).

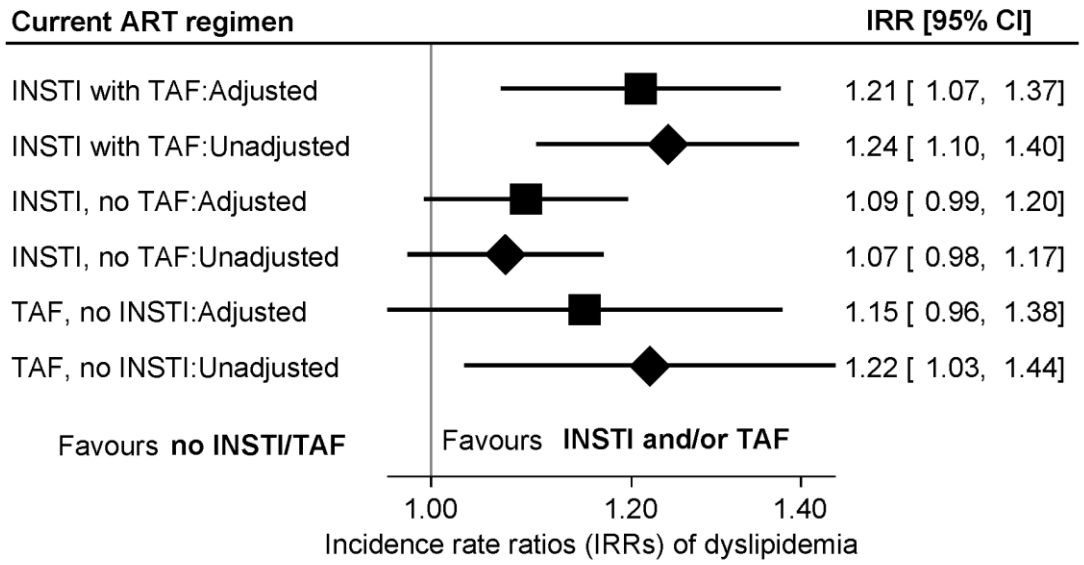
Incidence rate ratios of dyslipidemia in PLWH receiving combinations of INSTI and TAF versus those not receiving INSTI or TAF

In the univariate model, dyslipidemia was 24% (IRR 1.24, CI 1.10-1.40) and 22% (IRR 1.22, CI 1.03-1.44) more common in PLWH receiving TAF with and without INSTI, compared to those receiving neither INSTI nor TAF. In the multivariable model adjusted for all confounders but not time-updated BMI, the risk was attenuated in PLWH currently receiving TAF with INSTI (aIRR 1.21, CI 1.07-1.37) or without INSTI (1.19, CI 1.01-1.40), compared to those receiving regimens without TAF or INSTI. The inclusion of time-updated BMI in the multivariable model slightly further attenuated the risk of dyslipidemia in PLWH currently receiving TAF and INSTI (1.21, CI 1.07-1.37), while the incidence of dyslipidemia in those receiving TAF without INSTI became comparable to those without TAF or INSTI (1.15, CI 0.96-1.38). In both the univariable and multivariable models, the risk of dyslipidemia was consistently similar in participants receiving INSTIs without TAF versus regimens without INSTI

or TAF (Figure 2). The rates of dyslipidemia appeared to be higher in PLWH on TAF compared to non-TAF regimens across all BMI quintiles (Figure S4). The association between ART regimens and dyslipidemia did not differ by sex (*P*-interaction=0.286). Additionally, the risk of dyslipidemia increased with increasing time-updated BMI, and the association did not differ by ART regimens (P=0.303) (Table S6).



Panel A: Adjusted and unadjusted IRRs of hypertension in PLWH receiving combinations of INSTI with TAF versus those receiving contemporary regimens without INSTI or TAF.



Panel B: Adjusted and unadjusted IRRs of dyslipidemia in PLWH receiving combinations of INSTI with TAF versus those receiving contemporary regimens without INSTI or TAF.

Figure 2: Adjusted and unadjusted incident rate ratios (IRRs) of hypertension (panel A) and dyslipidemia (panel B) in PLWH currently receiving (i.e., time-updated) combinations of INSTI with TAF versus those receiving contemporary regimens without INSTI or TAF.

Caption for Figure 2

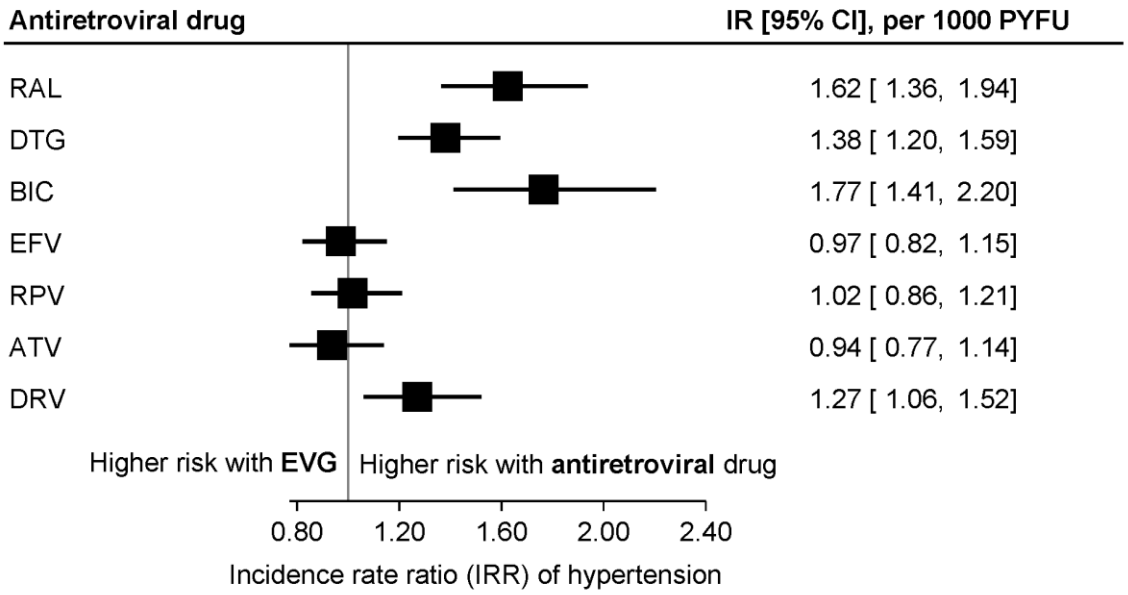
1. TAF-tenofovir alafenamide, INSTI-integrase strand transfer inhibitors, ART-antiretroviral therapy, IR-incidence rates (per 1000 person-years).

2. “INSTI with TAF” means regimen containing TAF and an INSTI, “INSTI, no TAF” means regimen containing INSTI but without TAF, “No INSTI, TAF” means regimen containing TAF but without INSTI “No INSTI/ TAF” means regimen containing without INSTI or TAF.
3. The multivariable model adjusted for baseline lipid and BP values, age, ethnicity, sex, baseline calendar year, smoking status, time-updated BMI, baseline diabetes mellitus status, prior AIDS, CVD, estimated glomerular filtration rate (eGFR), HIV RNA, CD4 nadir, and baseline CD4 counts, duration since HIV diagnosis, and cumulative exposure to potentially confounding ARVs (abacavir, nevirapine, stavudine, indinavir, and lopinavir). All covariates were prespecified *a priori*

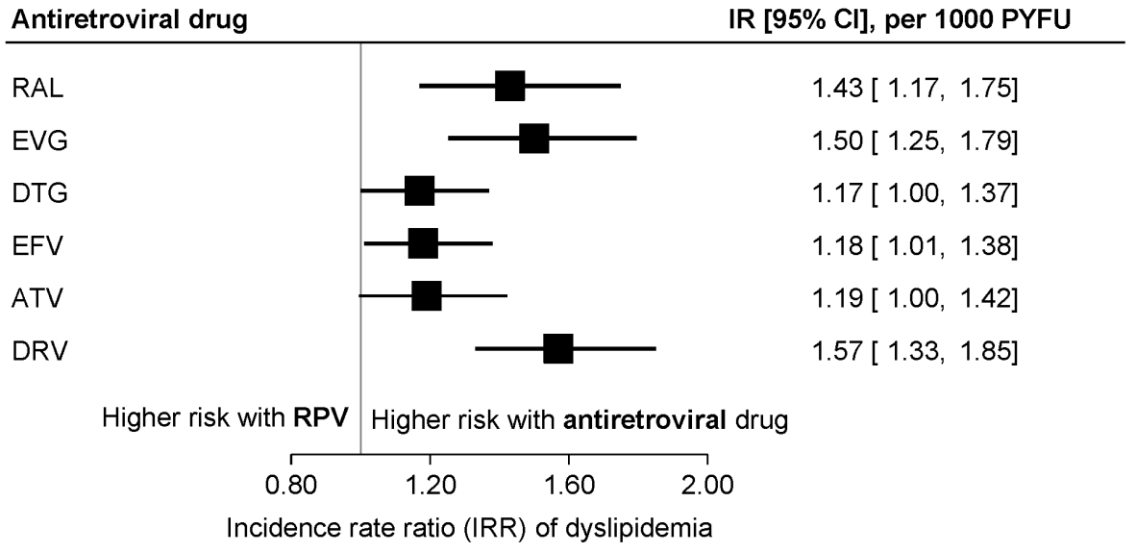
Use of individual antiretrovirals and risk of incident hypertension and dyslipidemia

There were more than 100 hypertension and dyslipidemia events for all ARVs (except bictegravir in the dyslipidemia analysis), and these were considered in the individual antiretroviral drug comparisons (Tables S3 and S4). In a multivariable model adjusted for time-updated BMI, NRTI backbone, and other confounders, the incidence of hypertension was higher in PLWH who were receiving BIC, RAL, DTG, or DRV than in those receiving EVG (Figure 3). ATV, EFV, and RPV were not associated with a higher risk of hypertension than EVG. EVG was chosen as the reference ARV because of its neutral effect on BMI[3]. The association between changes in BMI and hypertension did not differ by individual antiretrovirals (*P*-interaction=0.357).

In a full model adjusted for time-updated BMI, NRTI backbone, and other confounders, the incidence of dyslipidemia was higher in PLWH receiving DRV, EVG, RAL, EFV, and DTG than in those receiving RPV (Figure 3). Rilpivirine was chosen as a reference ARV because of its association with lower lipid levels[17]. The association between hypertension and changes in BMI did not statistically differ between individual antiretrovirals (*P*-interaction=0.185).



Panel A: Adjusted IRRs of hypertension in PLWH receiving antiretroviral drugs versus elvitegravir



Panel B: Adjusted IRRs of dyslipidemia in PLWH receiving antiretroviral drugs versus rilpivirine (RPV)

Figure 3: Adjusted incident rate ratios of hypertension (panel A) and dyslipidemia (panel B) in PLWH currently receiving individual antiretrovirals (time-updated) versus cobicistat-boosted elvitegravir (hypertension analysis) or rilpivirine (dyslipidemia analysis).

Caption for Figure 3

1. RAL-Raltegravir, EVG-elvitegravir (boosted with cobicistat), DTG-dolutegravir, BIC-bictegravir, EFV-efavirenz, RPV-rilpivirine, ATV-boosted atazanavir, DRV-darunavir, ART-antiretroviral therapy, IR-incidence rates (per 1000 person-years).

2. The reference antiretroviral drug in the hypertension analysis was cobicistat-boosted elvitegravir and rilpivirine in the dyslipidemia analysis.
3. The multivariable model was adjusted for the NRTI backbone, baseline lipid and BP values, age, ethnicity, sex, baseline calendar year, smoking status, time-updated BMI, baseline diabetes mellitus status, prior AIDS, CVD, estimated glomerular filtration rate (eGFR), HIV RNA, CD4 nadir, baseline CD4 counts, duration since HIV diagnosis, and cumulative exposure to potentially confounding ARVs (abacavir, nevirapine, stavudine, indinavir, and lopinavir). All covariates were prespecified *a priori*.

Sensitivity analyses

The results of the sensitivity analyses were broadly consistent, and there was no evidence to suggest that the association between BMI and hypertension or dyslipidemia differed between ART regimens (Tables S5 and S6).

DISCUSSION

This study examined the risk of hypertension and dyslipidemia in PLWH receiving INSTI and/or TAF-based regimens versus those receiving neither INSTI nor TAF. Our results suggest that current treatment with INSTIs and TAF is associated with hypertension and dyslipidemia, respectively. In addition, the attenuation in the risk of hypertension and dyslipidemia following adjustment for time-updated BMI suggests that the increased risk is partially mediated by weight gain. Finally, the risk of hypertension and dyslipidemia differed by individual antiretroviral drugs. The results were consistent across several sensitivity analyses.

Overall, the results are consistent with previous analyses that reported an association between exposure to INSTIs and increased BP or incident hypertension, albeit in selected populations and small cohorts[9,11–15]. However, the risk of hypertension appeared to be different for individual integrase inhibitors in the same class, similar to what was shown for other classes[31]. The risk of hypertension in PLWH receiving INSTI remained significant even after adjustment for time-updated weight gain, suggesting that additional non-weight related mechanisms may exist, as has been described for non-INSTI antiretroviral agents[32]. Therefore, the association and mechanisms underlying hypertension, weight gain, and cardiovascular risk in PLWH receiving INSTI should be investigated further. In addition, the association between weight gain and hypertension or dyslipidemia did not differ between ART regimens, suggesting that INSTI and/or TAF-associated

weight gain does not confer a comparatively higher risk of hypertension and dyslipidemia than weight gain from other causes. While reassuring, this finding emphasizes the need for hypertension and dyslipidemia monitoring in all PLWH, especially those who gain weight.

Furthermore, this analysis suggests that the current use of TAF with or without INSTI is associated with a higher risk of dyslipidemia, but this is probably due to weight gain following the withdrawal of the lipid-lowering effects of TDF, as also shown in other studies[20,33]. The risk of dyslipidemia became non-significant after adjustment for time-updated BMI, suggesting that dyslipidemia associated with TAF use is possibly mediated by weight gain. However, it is unclear whether other mechanisms of dyslipidemia previously described for other antiretrovirals[34] play an additional role in TAF-associated lipid level increases. Nevertheless, these results are consistent with studies that have linked TAF treatment with weight gain and increases in lipid levels[17,20,35]. Additionally, dyslipidemia rates were comparable regardless of whether TAF was used alone or concurrently with INSTIs, affirming the lipid-neutral effect of INSTIs described previously[16,17]. However, some studies have reported an increase in lipid levels in PLWH with INSTI-associated weight gain[18], suggesting that weight gain may lag behind clinical events by lengthy periods. Finally, our data also suggest that the risk of dyslipidemia differs by individual anchor antiretroviral drugs and is probably lowest with RPV, as has been similarly demonstrated in other studies[17,36].

The present analysis has several limitations, and the results do not suggest a causal relationship. First, data on BMI, BP, and lipid levels were lacking in some cohorts. Second, this analysis assumes that fitting models with time-updated BMI captures any increased risk of hypertension and dyslipidemia due to BMI increases; however, follow-up between INSTI-related BMI change and the clinical events may be too short to capture the association. Third, data was missing on diet, physical activity, and family history. Fourth, BP and lipid monitoring are not standardized across cohorts, and hypertension and lipid monitoring appear to be targeted, with almost half of the participants missing BP and lipid results, respectively. However, it is not clear how such targeted monitoring would favor certain drugs or classes. Fifth, despite cabotegravir and doravirine being increasingly used, we did not have sufficient data to analyse these agents (and BIC in the dyslipidemia analysis). Finally, there may be potential channeling bias with patients at high cardiovascular risk being preferentially initiated

on INSTI-based regimens, as was suggested in another RESPOND analysis[37]. However, we compared PLWH who received INSTIs during follow-up versus those who consistently received non-INSTIs, and we found no evidence to suggest channeling bias. In addition, we adjusted for several confounders, although residual confounding cannot be entirely excluded. Despite the limitations, the analysis provides a signal based on routinely collected clinic-based from a large heterogeneous cohort with long follow-up.

In conclusion, we report an association between weight gain and concurrent or separate use of INSTIs or TAF and hypertension and dyslipidemia. The association between INSTIs and hypertension appears to be partially mediated by weight gain. Furthermore, the association between weight gain and hypertension or dyslipidemia was not different in regimens with INSTI or TAF than in other contemporary antiretroviral regimens. Interpreted with results from a previous analysis in the RESPOND cohort that reported an immediate increase in cardiovascular mortality in PLWH receiving INSTIs[37], further research is warranted to fully understand the associations between the use of INSTI and TAF, weight gain, CVD risk factors, and CVD risk.

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Authors' contributions: DMB, supervised by KP, MNP, and MLP, conceived the idea and developed the project proposal and a statistical analysis plan. LR, AM, and LB also provided

additional input into the proposal and the analysis plan. All authors reviewed the proposal and contributed to the revised proposal and analysis plan. DMB, under the supervision of KP and ML, performed the statistical analysis and wrote the analysis report, which was reviewed and commented on by all authors. DMB developed the first draft of the manuscript and revised the subsequent drafts. DMB, KP, MNP and ML reviewed all manuscript versions and interpreted the data. FM, AR, KP, FW, SDW, AC, ADM, CM, JW, EF, IA, MS, LB, NJ, AVA, VV, CC, EB, AM, and LR contributed to the interpretation of the data and reviewed and provided input into the final draft of the manuscript.

Conflict of interest: AM has received travel support, lecture fees and consultancy fees from Gilead, ViiV, Eiland and Bonnin, all outside the submitted work. VV, CC and EB are employees of ViiV Healthcare, Gilead Sciences, and MSD, respectively. The rest of the authors have declared no conflict of interest.

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REFERENCES

1. World Health Organization. Update on the transition to dolutegravir-based antiretroviral therapy: report of a WHO meeting, 29–30 March 2022. 2022. Available at: https://www.who.int/publications/i/item/9789240053335.

2. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: Risk factors in randomized comparative clinical trials. Clinical Infectious Diseases **2020**;

3. Bansi-Matharu L, Phillips A, Oprea C, et al. Contemporary antiretrovirals and body-mass index: a prospective study of the RESPOND cohort consortium. Lancet HIV **2021**; 8:e711–e722.

4. Bai R, Lv S, Wu H, Dai L. Effects of different integrase strand transfer inhibitors on body weight in patients with HIV/AIDS: a network meta-analysis. BMC Infect Dis **2022**; 22.

5. Hester EK, Greenlee S, Durham SH. Weight Changes With Integrase Strand Transfer Inhibitor Therapy in the Management of HIV Infection: A Systematic Review. Annals of Pharmacotherapy **2022**; 56:1237–1249.

6. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. New England Journal of Medicine **2019**;

7. Antonello VS, Carlos Ferreira Antonello I, Grossmann TK, Tovo CV, Brasil Dal Pupo B, De Quadros Winckler L. Hypertension - An emerging cardiovascular risk factor in HIV infection. Journal of the American Society of Hypertension **2015**; 9:403–407.

8. Bannister WP, Mast TC, de Wit S, et al. Changes in body mass index and clinical outcomes after initiation of contemporary antiretroviral regimens. AIDS **2022**; 36:2107–2119.

9. Galdamez R, García JA, Fernández M, et al. Short-term increase in risk of overweight and concomitant systolic blood pressure elevation in treatment-Naïve Persons starting INSTI-based antiretroviral therapy. Open Forum Infect Dis **2019**;

10. Achhra AC, Mocroft A, Reiss P, et al. Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: The D: A: D study. HIV Med **2016**; 17:255–268.

11. Summers NA, Lahiri CD, Angert CD, et al. Metabolic Changes Associated With the Use of Integrase Strand Transfer Inhibitors Among Virally Controlled Women. Journal of Acquired Immune Deficiency Syndrome **2020**;

12. Brennan AT, Nattey C, Venter F, et al. Change in Body Weight and Risk of Hypertension after Switching from Efavirenz to Dolutegravir in Adults Living with HIV: Evidence from Routine Care in Johannesburg, South Africa. EClinicalMedicine **2022**; 57.

13. Saums MK, King CC, Adams JC, et al. Combination Antiretroviral Therapy and Hypertensive Disorders of Pregnancy. Obstetrics and Gynecology **2019**; 134:1205–1214.

14. Zash R, Caniglia EC, Diseko M, et al. Maternal weight and birth outcomes among women on antiretroviral treatment from conception in a birth surveillance study in Botswana. J Int AIDS Soc **2021**; 24:e25763.

15. Masenga SK, Povia JP, Mutengo KH, et al. Sex differences in hypertension among people living with HIV after initiation of antiretroviral therapy. Front Cardiovasc Med **2022**; 9:1006789.

16. Snedecor SJ, Radford M, Kratochvil D, Grove R, Punekar YS. Comparative efficacy and safety of dolutegravir relative to common core agents in treatment-naïve patients infected with HIV-1: A systematic review and network meta-analysis. BMC Infect Dis **2019**;

17. Byonanebye DM, Polizzotto MN, Begovac J, et al. Incidence of dyslipidemia in people with HIV who are treated with integrase inhibitors versus other antiretroviral agents. AIDS **2021**; 35:869–882.

18. Rizzardo S, Lanzafame M, Lattuada E, et al. Dolutegravir monotherapy and body weight gain in antiretroviral naïve patients. AIDS **2019**; 33:1673–1674.

19. Palella FJ, Hou Q, Li J, et al. Weight Gain and Metabolic Effects in Persons With HIV Who Switch to ART Regimens Containing Integrase Inhibitors or Tenofovir Alafenamide. JAIDS Journal of Acquired Immune Deficiency Syndromes **2023**; 92.

20. Surial B, Mugglin C, Calmy A, et al. Weight and Metabolic Changes After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in People Living With HIV. Ann Intern Med **2021**; 174:758–767.

21. Wit F, Reiss P, Hillebregt M, et al. How to RESPOND to modern challenges for people living with HIV: A profile for a new cohort consortium. Microorganisms **2020**; 8:1–17.

22. Wharton S, Raiber L, Serodio KJ, Lee J, Christensen RAG. Medications that cause weight gain and alternatives in Canada: a narrative review. Diabetes Metab Syndr Obes **2018**; 11:427..

23. Hatleberg CI, Ryom L, d'Arminio Monforte A, et al. Association between exposure to antiretroviral drugs and the incidence of hypertension in HIV-positive persons: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. HIV Med **2018**; 19:605–618.

24. Byonanebye DM, Polizzotto MN, Neesgaard B, et al. Incidence of hypertension in people with HIV who are treated with integrase inhibitors versus other antiretroviral regimens in the RESPOND cohort consortium. HIV Med **2022**; 00:1–16.

25. Kamara DA, Smith C, Ryom L, et al. Longitudinal analysis of the associations between antiretroviral therapy, viraemia and immunosuppression with lipid levels: the D:A:D study. Antivir Ther **2016**; 21:495–506.

26. van Zoest RA, Wit FW, Kooij KW, et al. Higher Prevalence of Hypertension in HIV-1-Infected Patients on Combination Antiretroviral Therapy Is Associated With Changes in Body Composition and Prior Stavudine Exposure. Clin Infect Dis **2016**; 63:205–213.

27. Kim J, Bang JH, Shin JY, Yang BR, Lee J, Park BJ. Hypertension Risk with Abacavir Use among HIV-Infected Individuals: A Nationwide Cohort Study. Yonsei Med J **2018**; 59:1245.

28. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2022.

29. Francois Venter WD, Sokhela S, Calmy A, et al. Weight gain stopping/switch rules for antiretroviral clinical trials. AIDS **2021**; 35:S183–S188..

30. Shah S, Pilkington V, Hill A. Is tenofovir disoproxil fumarate associated with weight loss? AIDS **2021**; 35:S189–S195..

31. Hatleberg CI, Ryom L, d'Arminio Monforte A, et al. Association between exposure to antiretroviral drugs and the incidence of hypertension in HIV-positive persons: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. HIV Med **2018**; 19:605–618.

32. Fahme SA, Bloomfield GS, Peck R. Hypertension in HIV-Infected Adults. Hypertension **2018**;

33. Mallon PWG, Brunet L, Fusco JS, et al. Lipid Changes after Switch from TDF to TAF in the OPERA Cohort: LDL Cholesterol and Triglycerides. Open Forum Infect Dis **2022**; 9:ofab621.

34. Richmond SR, Carper MJ, Lei X, Zhang S, Yarasheski KE, Ramanadham S. HIV-protease inhibitors suppress skeletal muscle fatty acid oxidation by reducing CD36 and CPT1 fatty acid transporters. Biochim Biophys Acta Mol Cell Biol Lipids **2010**; 1801:559–566.

35. Lacey A, Savinelli S, Barco EA, et al. Investigating the effect of antiretroviral switch to tenofovir alafenamide on lipid profiles in people living with HIV. AIDS **2020**; 34:1161–1170.

36. Gatechompol S, Avihingsanon A, Apornpong T, Han WM, Kerr SJ, Ruxrungtham K. Efficacy and improvement of lipid profile after switching to rilpivirine in resource limited setting: real life clinical practice. AIDS Res Ther **2019**;

37. Neesgaard B, Greenberg L, Miró JM, et al. Associations between integrase strand-transfer inhibitors and cardiovascular disease in people living with HIV: a multicentre prospective study from the RESPOND cohort consortium. Lancet HIV **2022**;

SUPPLEMENTARY TABLES AND FIGURES

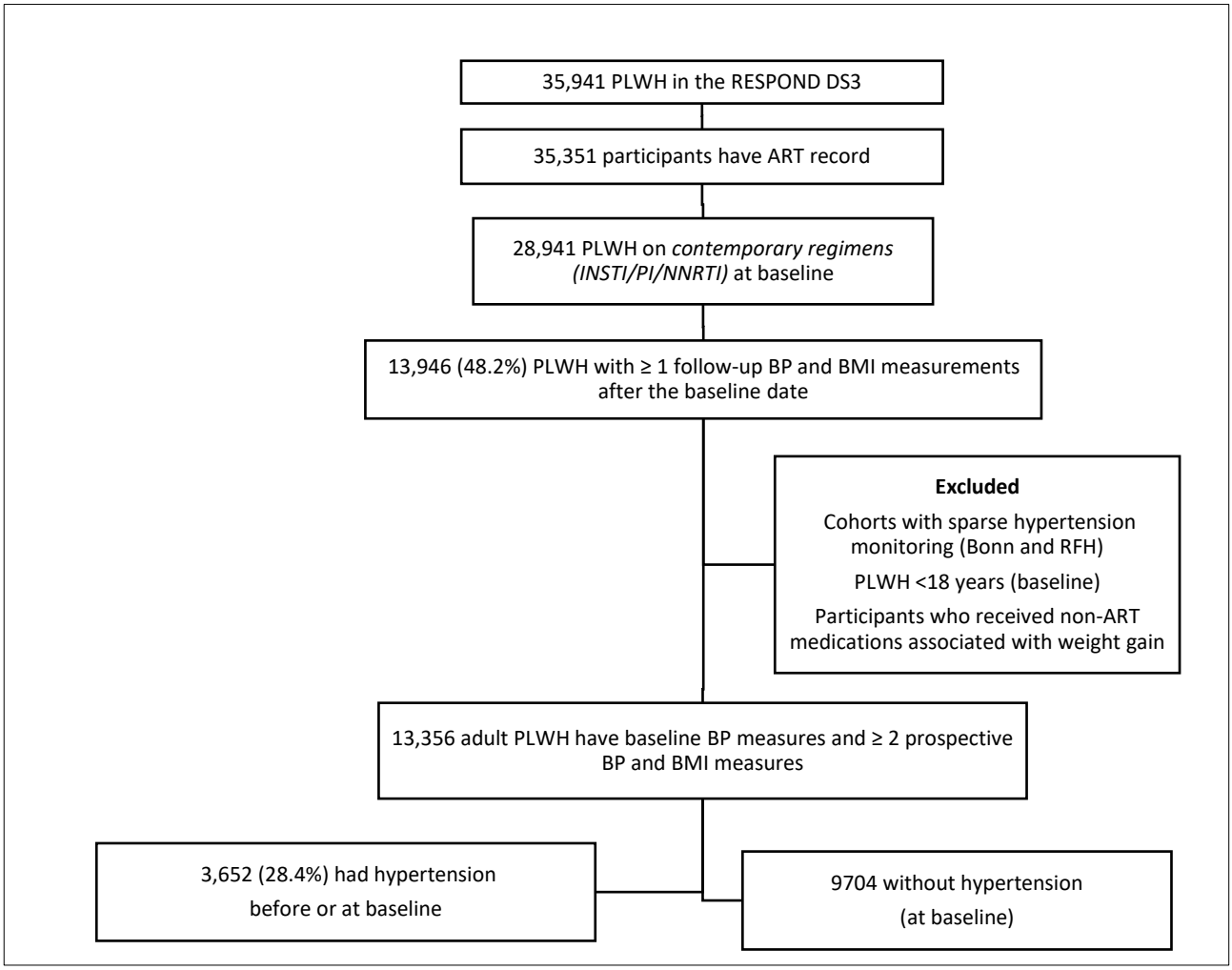

Figure S1. Participant inclusion in the hypertension analysis

Caption for Figure S1

1. PLWH-people living with HIV, BMI-body mass index, INSTI-integrase strand transfer inhibitors, TAF-tenofovir alafenamide, BMI-body mass index, ART-antiretroviral therapy, PIs-Protease inhibitors, NNRTI-non-nucleoside reverse transcriptase inhibitors.

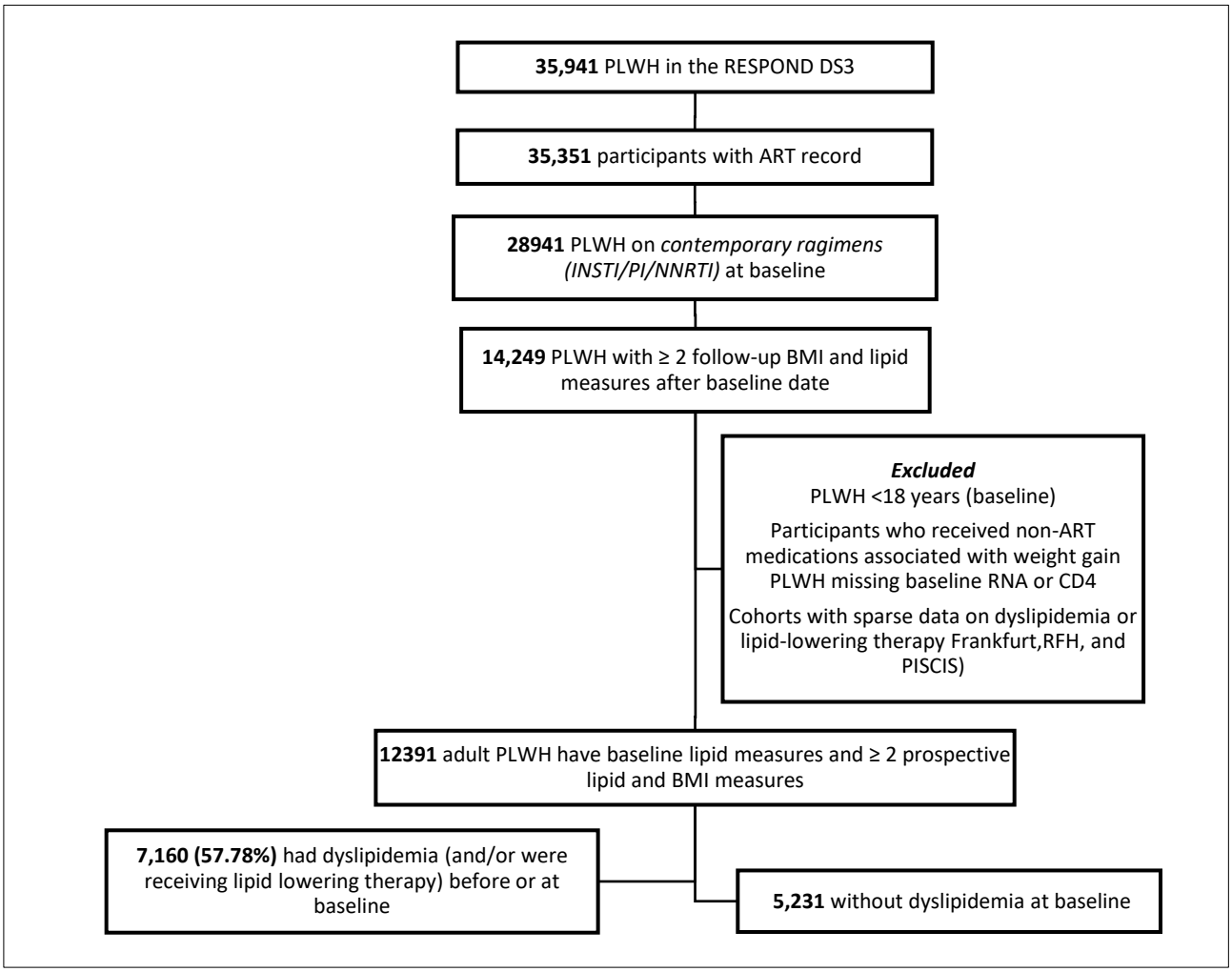

Figure S2. Participant inclusion in the dyslipidemia analysis

Caption for Figure S2

2. PLWH-people living with HIV, BMI-body mass index, INSTI-integrase strand transfer inhibitors, TAF-tenofovir alafenamide, BMI-body mass index, ART-antiretroviral therapy regimens, PIs-Protease inhibitors, NNRTI-n on-nucleoside reverse transcriptase inhibitors.

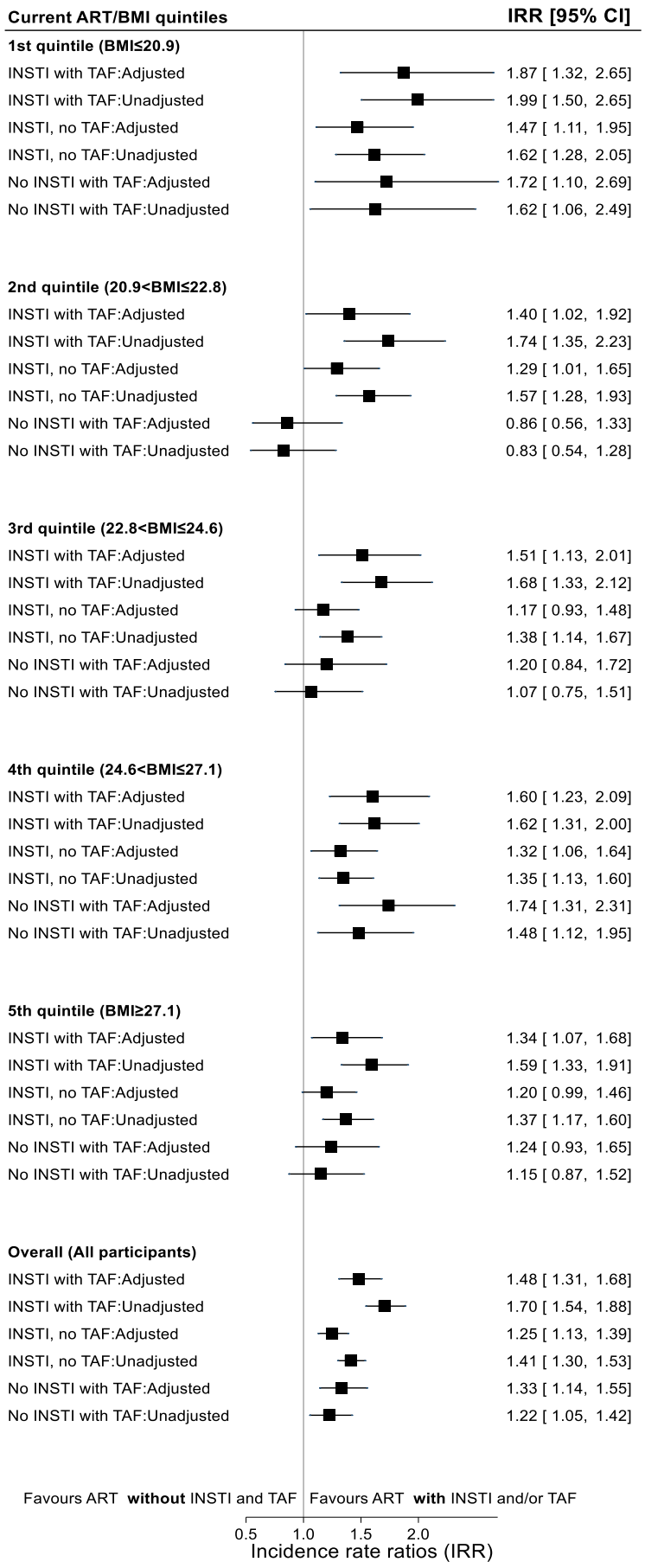

Figure S3: Adjusted and unadjusted IRRs of hypertension, stratified by quintiles of time-updated BMI in PLWH receiving ART combinations of INSTI and TAF versus those receiving contemporary regimens without INSTI or TAF

Caption for Figure S3

3. IRR-incidence rate ratios, INSTI-integrase strand transfer inhibitors, TAF-tenofovir alafenamide, BMI-body mass index, ART-antiretroviral therapy regimens.
4. The reference ART regimen is PLWH receiving regimens without INSTI or TAF.
5. The multivariable model was adjusted for the NRTI backbone, baseline lipid and BP values, age, ethnicity, sex, baseline calendar year, smoking status, baseline BMI, baseline diabetes mellitus status, prior AIDS, CVD, estimated glomerular filtration rate (eGFR), HIV RNA, CD4 nadir, baseline CD4 counts, duration since HIV diagnosis, and cumulative exposure to potentially confounding ARVs (abacavir, nevirapine, stavudine, indinavir, and lopinavir). All covariates were prespecified *a priori*.

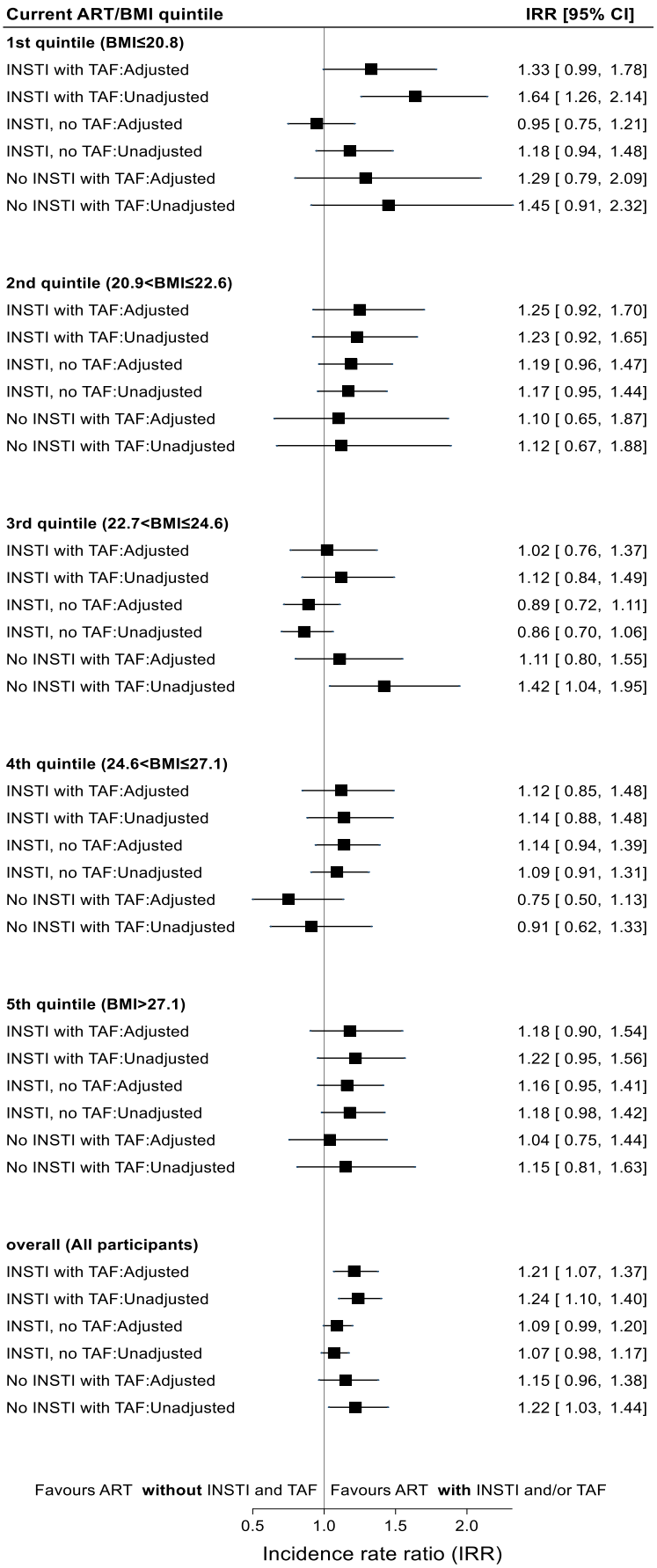

Figure S4: Adjusted and unadjusted IRRs of dyslipidemia, overall and stratified by quintiles of time-updated BMI, in PLWH receiving ART combinations of INSTI and TAF versus those receiving contemporary regimens without INSTI or TAF

Caption for Figure S4

1. IRR-incidence rate ratios, INSTI-integrase strand transfer inhibitors, TAF-tenofovir alafenamide, BMI-body mass index, ART-antiretroviral therapy regimens.
2. The reference ART regimen is PLWH receiving regimens without INSTI or TAF.
3. The multivariable model was adjusted for the NRTI backbone, baseline lipid and BP values, age, ethnicity, sex, baseline calendar year, smoking status, baseline BMI, baseline diabetes mellitus status, prior AIDS, CVD, estimated glomerular filtration rate (eGFR), HIV RNA, CD4 nadir, baseline CD4 counts, duration since HIV diagnosis, and cumulative exposure to potentially confounding ARVs (abacavir, nevirapine, stavudine, indinavir, and lopinavir). All covariates were prespecified *a priori*.

Table S1: Characteristics of participants included in the hypertension incidence analysis who received INSTI during follow-up versus those who received regimens without INSTI

Variable	Categories†	INSTI during follow-up (n=6,086)		No INSTI during follow-up (n=3,618)		Total (n=9,704)	
		n	%	n	%	n	%
Gender	Male	1,529	25.1	848	23.4	2,377	24.5
	Female	4,557	74.9	2,770	76.6	7,327	75.5
Ethnicity	White	4,313	70.9	2,640	73.0	6,953	71.7
	Black	452	7.4	372	10.3	824	8.5
	Other/Unknown	1,321	21.7	606	16.8	1,927	19.9
Region	W. Europe	3,486	57.3	1,717	47.5	5,203	53.6
	S. Europe	495	8.1	345	9.5	840	8.7
	N. Europe*	2,105	34.6	1,556	43.0	3,661	37.7
Route of HIV acquisition	MSM	783	12.9	437	12.1	1,220	12.6
	IDU	2,987	49.1	1,764	48.8	4,751	49.0
	Heterosexual	1,961	32.2	1,269	35.1	3,230	33.3
	Other/Unknown	355	5.8	148	4.1	503	5.2
Treatment experience	Naive	1,524	25.0	664	18.4	2,188	22.6
	Experienced	4,562	75.0	2,954	81.7	7,516	77.5
Prior AIDS	Yes	1,207	19.8	764	21.1	1,971	20.3
	No	4,879	80.2	2,854	78.9	7,733	79.7
Hepatitis B infection	Positive	290	4.8	214	5.9	214	5.9
	Negative	5,323	87.5	3,051	84.3	8,374	86.3
	Unknown	473	7.8	353	9.8	826	8.5
Hepatitis C infection	Positive	3,842	63.1	2,373	65.6	6,215	64.1
	Negative	1,293	21.3	711	19.7	2,004	20.7
	Unknown	951	15.6	951	15.6	1,485	15.3
Smoking Status	Current	2,021	33.2	1,254	34.7	3,275	33.8
	Prior	807	13.3	409	11.3	1,216	12.5
	Never	2,037	33.5	1,439	39.8	3,476	35.8
	Unknown	1,221	20.1	516	14.3	1,737	17.9
Chronic Kidney Disease	Yes	547	9.0	225	6.2	772	8.0
	No	5,523	90.8	3,376	93.3	8,899	91.7
	Unknown	16	0.3	17	0.5	33	0.3
Diabetes Mellitus	Yes	201	3.3	144	4.0	345	3.6
	No	5,628	92.5	3,304	91.3	8,932	92
	Unknown	257	4.2	170	4.7	427	4.4
Cardiovascular disease	Yes	46	0.8	4	0.1	50	0.5
	No	5,583	91.7	3,287	90.9	8,870	91.4
	Unknown	457	7.5	327	9.0	784	8.1
Lipid-lowering therapy	Yes	227	3.7	106	2.9	333	3.4
	No	5,859	96.3	3,512	97.1	9,371	96.6
		Median (IQR)	**# missing (%)**	**Median (IQR)**	**# missing (%)**	**Median (IQR)**	**# missing (%)**
Age (years)		45(36,52)	0(0)	43(35,50)	0(0)	44(36,51)	0(0)
Baseline CD4 (cells/μL)		554(364,754)	0(0)	529(373,708)	0(0)	544(367,739)	0(0)
Nadir CD4 (cells/μL)		244(118,387)	0(0)	250(136,367)	0(0)	246(125,379)	0(0)
Baseline HIV RNA (copies/mL)		39(19,851)	0(0)	39(19,138)	0(0)	39(19,367)	0(0)
Baseline BMI (kg/m^2)		23.3(21.1,25.7)	0(0)	23.6(21.5,26.1)	0(0)	23.4(21.2,25.9)	0(0)
Baseline HDL (mg/dL)		46(37,58)	705(11.6)	47(38,58)	445(12.3)	46(38,58)	1150(11.9)
Baseline TCHOL (mg/dL)		182(155,211)	441(7.3)	186(159,216)	202(5.6)	183(155,213)	643(6.6)
Baseline TRIG (mg/dL)		119(83,175)	511(8.4)	115(80,171)	301(8.3)	117(82,174)	812(8.37)
Baseline LDL (mg/dL)		106(84,130)	3650(60.0)	108(87,133)	2360(65.2)	106(85,132)	6010(61.9)
Baseline GFR mL/min/1.73 m^2		99(84,111)	528(8.7)	103(90,113)	188(5.2)	101(86,112)	716(7.4)
Baseline DBP (mmHg)		77(70,82)	0(0)	78(70,82)	0(0)	78.0(70,82)	0(0)
Baseline SBP (mmHg)		121(113,130)	0(0)	120(114,130)	0(0)	121(114,130)	0(0)
ART duration (years)		9.1(4.2,15.1)	1524(25.0)	10.7(5.9,16.1)	664(18.4)	9.8(4.9,15.6)	2188(22.6)
5-year predicted CVD risk		2.1(1.0,4.1)	5329(12.4)	2.0(0.9,3.9)	452(12.5)	2.1(1.0,4.0)	1209(12.5)
Number of follow-up BP results		9(5,13)	0(0)	10(5,16)	0(0))	9(5,14)	0(0)
Baseline date (mm-yy)		07/15(05/14,10/16)	0(0)	01/12(01/12,04/13)	0(0)	09/14(01/12,03/16)	0(0)
Cumulative exposure to antiretroviral agents (years)**		**Median (IQR)**	**# exposed (%)**	**Median (IQR)**	**# exposed (%)**	**Median (IQR)**	**# exposed (%)**
Cumulative exposure to NRTIs		8.9(4.2,14.8)	4528(74.4)	10.4(5.8,15.6)	2951(81.6)	9.6(4.8,15.1)	7479(77.1)
Cumulative exposure to NNRTIs		4.6(1.5,9.3)	2727(44.8)	7.7(3.4,12.4)	2129(58.8)	6.0(2.1,10.8)	4856(50.0)
Cumulative exposure to PIs		6.4(2.6,11.3)	3478(57.2)	6.6(2.6,12.5)	1958(54.1)	6.5(2.6,11.7)	5436(56.0)
Cumulative exposure to abacavir		4.5(1.5,8.6)	1889(31.0)	5.5(2.2,9.7)	905(25.0)	4.8(1.7,9.0)	2794(28.8)
Cumulative exposure to stavudine		3.2(1.5,5.1)	1152(18.9)	3.5(1.4,5.8)	712(19.7)	3.3(1.5,5.4)	1864(19.2)
Cumulative exposure to nevirapine		1.8(0.3,6.6)	895(14.7)	1.3(0.2,4.5)	371(10.3)	1.8(0.3,6.0)	1266(13.1)
Cumulative exposure to efavirenz		4.4(1.2,8.9)	2020(33.2)	8.1(3.5,12.5)	1827(50.5)	6.1(1.9,10.8)	3847(39.6)
Cumulative exposure to atazanavir		4.9(1.9,8.1)	1458(24.0)	6.0(2.6,9.5)	961(26.6)	5.4(2.1,8.6)	2419(24.9)
Cumulative exposure to darunavir		3.0(1.1,4.9)	1397(23.0)	5.3(2.3,8.2)	652(18.0)	3.4(1.4,5.8)	2049(21.1)
Cumulative exposure to indinavir		1.7(0.7,3.4)	712(11.7)	2.1(0.9,4.1)	453(12.5)	1.8(0.7,3.6)	1165(12.0)
Cumulative exposure to lopinavir		3.2(1.1,6.9)	1516(24.9)	1.9(0.7,4.2)	680(18.8)	2.8(0.9,6.1)	2196(22.6)
Cumulative exposure to TDF‖		5.7(2.7,8.5)	3633(59.7)	7.2(3.9,10.8)	2380(65.8)	6.2(3.1,9.4)	6013(62.0)

Caption for Table S1

1. INSTI-integrase inhibitors, PI-Protease inhibitors, NRTI-nucleosi(t)de reverse transcriptase inhibitors, NNRTI-non-nucleoside reverse transcriptase inhibitors; CVD-cardiovascular disease, eGFR-estimated

glomerular filtration rate (GFR), using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, HDL-high-density lipoprotein, LDL-low-density lipoprotein (LDL), TCHOL-total cholesterol, TRIG-triglycerides, IDU-intravenous drug use, MSM-men who have sex with men, SBP-systolic blood pressure, DBP-diastolic blood pressure, ART-antiretroviral therapy.

2. All lipids are expressed in mg/dL. To convert triglyceride levels from mg/dL to mmol/L, divide by 88.57. For HDL, LDL, and total cholesterol, divide by 38.67.
3. Note *including Australia.
4. **The stated ART duration and cumulative exposure period is for participants receiving ART before baseline. Exposure to TAF at baseline is not shown because TAF was approved in Europe in 2017 (after the baseline date).
5. †Other categories (other than those stated), including unknown status.
6. ‖Tdf-tenofovir disoproxil fumarate

Table S2: Characteristics of participants included in the dyslipidemia incidence analysis who received INSTI during follow-up versus those who did not

Variable	Categories	INSTI during follow-up (n=2,716)		No INSTI during follow-up (n= 2,515)		Total (n=5,231)	
		n	%	n	%	n	%
Gender	Female	758	27.9	677	26.9	1,435	27.4
	Male	1,958	72.1	1,838	73.1	3,796	72.6
Ethnicity	White	1,843	67.9	1,859	73.9	3,702	70.8
	Black	299	11.0	284	11.3	583	11.2
	Other/Unknown	574	21.1	372	14.8	946	18.1
Region	W. Europe	1,520	56.0	1,197	47.6	2,717	51.9
	S. Europe	316	11.6	276	11.0	592	11.3
	N. Europe*	880	32.4	1,042	41.4	1,922	36.7
Route of HIV acquisition	MSM	1,321	48.6	1,159	46.1	2,480	47.4
	IDU	318	11.7	323	12.8	641	12.3
	Heterosexual	933	34.4	910	36.2	1,843	35.2
	Other/Unknown	144	5.3	123	4.9	267	5.1
Treatment experience	Naive	886	32.6	443	17.6	1,329	25.4
	New Class	1,830	67.4	2,072	82.4	3,902	74.6
Prior AIDS	Yes	462	17.0	520	20.7	982	18.8
	No	2,254	83.0	1,995	79.3	4,249	81.2
Hepatitis B infection	Positive	123	4.5	165	6.6	288	5.5
	Negative	2,347	86.4	2,098	83.4	4,445	85.0
	Unknown	246	9.1	252	10.0	498	9.5
Hepatitis C infection	Positive	532	19.6	505	20.1	1,037	19.8
	Negative	1,824	67.2	1,682	66.9	3,506	67.0
	Unknown	360	13.3	328	13.0	688	13.2
Smoking Status	Current	795	29.3	811	32.3	1,606	30.7
	Prior	310	11.4	285	11.3	595	11.4
	Never	990	36.5	1,015	40.4	2,005	38.3
	Unknown	621	22.9	404	16.1	1,025	19.6
Chronic Kidney Disease	Yes	203	7.5	136	5.4	339	6.5
	No	2,505	92.2	2,376	94.5	4,881	93.3
	Unknown	8	0.3	3	0.1	11	0.2
Diabetes Mellitus	Yes	55	2.0	84	3.3	139	2.7
	No	2,559	94.2	2,321	92.3	4,880	93.3
	Unknown	102	3.8	110	4.4	212	4.1
Cardiovascular disease	Yes	15	0.6	1	0.04	16	0.3
	No	2,417	88.0	2,272	90.3	4,689	89.6
	Unknown	284	10.5	242	9.6	526	10.1
		Median (IQR)	**# missing (%)**	**Median (IQR)**	**# missing (%)**	**Median (IQR)**	**# missing (%)**
Age (years)		43(34,51)	0(0)	42(35,50)	0(0)	43(35,50)	0(0)
Baseline CD4 (cells/μL)		525(340,723)	0(0)	517(370,686)	0(0)	520(356,709)	0(0)
Nadir CD4 (cells/μL)		265(137,421)	0(0)	251(144,368)	0(0)	258(140,393)	0(0)
Baseline HIV RNA (copies/mL)		39(19,5826)	0(0)	36(19,89)	0(0)	39(19,499)	0(0)
Baseline BMI (kg/m^2)		23.0(20.8,25.6)	0(0)	23.5(21.5,26.2)	0(0)	23.3(21.1,25.8)	0(0)
Baseline HDL (mg/dL)		52(43,63)	244(9.0)	51(43,62)	244(9.7)	52(43,62)	488(9.3)
Baseline TCHOL (mg/dL)		173(151,195)	10(0.4)	182(157,203)	16(0.6)	177(155,199)	26(0.5)
Baseline TRIG (mg/dL)		90(68,123)	73(2.7)	97(71,133)	111(4.4)	94(71,127)	184(3.5)
Baseline LDL (mg/dL)		100(82,120)	1432(52.7)	104(88,123)	1601(63.7)	101(84,122)	3033(58.0)
Baseline GFR ml/min/1.73 m^2		101(87,113)	228(8.4)	104(91,115)	140(5.6)	103(89,114)	368(7.0)
Baseline DBP (mmHg)		80(70,85)	150(5.5)	79(70,85)	135(5.4)	80(70,85)	285(5.5)
Baseline SBP (mmHg)		124(115,136)	150(5.5)	124(115,135)	135(5.4)	124(115,135)	285(5.5)
ART duration (years)		8.5(3.8,14.8)	886(32.6)	10.4(5.8,15.3)	443(17.6)	9.6(4.8,15.0)	1329(25.4)
5-year predicted CVD risk (%)		1.6(0.7,3.1)	360(13.3)	1.7(0.8,3.4)	358(14.2)	1.7(0.8,3.2)	718(13.7)
Number of follow-up lipid results		9(5,13)	0(0)	11(6,17)	0(0)	10(5,15)	0(0)
Baseline date (mm/yy)		09/15(07/14,02/17)	0(0)	01/12(01/12,07/13)	0(0)	05/14(01/12,03/16)	0(0)
Cumulative exposure to antiretroviral agents (years)**		**Median (IQR)**	**# exposed (%)**	**Median (IQR)**	**# exposed (%)**	**Median (IQR)**	**# exposed (%)**
Cumulative exposure to NRTIs		8.4(3.7,14.5)	1823(67.1)	10.1(5.7,15.0)	2069(82.3)	9.4(4.7,14.8)	3892(74.4)
Cumulative exposure to NNRTIs		4.7(1.5,9.4)	1118(41.2)	7.8(3.6,12.1)	1538(61.2)	6.4(2.4,11.2)	2656(50.8)
Cumulative exposure to PIs		5.7(2.2,10.3)	1295(47.7)	6.4(2.7,11.1)	1284(51.1)	6.0(2.4,10.7)	2579(49.3)
Cumulative exposure to ABC		4.1(1.3,8.5)	707(26.0)	5.3(2.2,9.8)	582(23.1)	4.5(1.7,9.0)	1289(24.6)
Cumulative exposure to d4T		3.0(1.2,4.9)	393(14.5)	3.4(1.2,5.9)	420(16.7)	3.2(1.2,5.4)	813(15.5)
Cumulative exposure to NVP		2.1(0.2,6.1)	336(12.4)	1.0(0.2,3.8)	225(9.0)	1.5(0.2,5.3)	561(10.7)
Cumulative exposure to EFV		4.6(1.4,9.3)	853(31.4)	8.2(3.7,12.3)	1370(54.5)	6.7(2.6,11.4)	2223(42.5)
Cumulative exposure to AZV		4.8(1.7,7.7)	551(20.3)	6.0(2.8,9.5)	660(26.2)	5.5(2.3,8.8)	1211(23.2)
Cumulative exposure to DRV		2.6(0.8,4.6)	525(19.3)	4.7(2.3,7.0)	387(15.4)	3.2(1.3,5.8)	912(17.4)
Cumulative exposure to IDV		1.8(0.8,3.4)	273(10.1)	2.1(0.9,4.6)	268(10.7)	2.0(0.8,3.9)	541(10.3)
Cumulative exposure to LPV		2.5(0.7,5.9)	511(18.8)	1.9(0.7,4.2)	406(16.1)	2.2(0.7,5.1)	917(17.5)

Caption for Table S2

1. INSTI-integrase inhibitors, PI-Protease inhibitors, NRTI-nucleosi(t)de reverse transcriptase inhibitors, NNRTI-non-nucleoside reverse transcriptase inhibitors; CVD-cardiovascular disease, eGFR-estimated glomerular filtration rate (GFR), using the race-neutral Chronic Kidney Disease Epidemiology

Collaboration (CKD-EPI) equation, HDL-high-density lipoprotein, LDL-low-density lipoprotein (LDL), TCHOL-total cholesterol, TRIG-triglycerides, IDU-intravenous drug use, MSM-men who have sex with men, SBP-systolic blood pressure, DBP-diastolic blood pressure, ART-antiretroviral therapy.

2. All lipids are expressed in mg/dL. To convert triglyceride levels from mg/dL to mmol/L, divide by 88.57. For HDL, LDL, and total cholesterol, divide by 38.67.
3. Note *including Australia.
4. **The stated ART duration and cumulative exposure period is for participants receiving ART before baseline. Exposure to TAF at baseline is not shown because TAF was approved in Europe in 2017 (after the baseline date).
5. †Other categories (other than those stated), including unknown status.

Table S3: Incident hypertension events in PLWH receiving individual antiretrovirals

Antiretroviral drug	Person-years	Number of events	Rate
Raltegravir	2939.9	293	100(89,112)
Elvitegravir	4271.2	285	67(59,75)
Dolutegravir	10053.2	947	94(88,100)
Bictegravir *	943.2	112	119(99,143)
Efavirenz	7095.9	409	58(52,64)
Rilpivirine	5080.4	299	59(53,66)
Atazanavir	3487	205	59(51,67)
Darunavir	4800.2	326	68(61,76)
Other*	1322.2	101	76(63,93)
Total	39993.2	2977	74(72,77)

**Non-contemporary regimens ("others") we not included in the antiretroviral comparisons (<100 events)*

Table S4: Incident dyslipidemia events in PLWH receiving individual antiretrovirals

Antiretroviral drug	Person-years	Number of events	Rate
Raltegravir	1139.1	185	162.4(140.6,187.6)
Elvitegravir	1664.2	275	165.2(146.8,186)
Dolutegravir	4425.1	588	132.9(122.6,144.1)
Bictegravir *	539.8	86	159.3(129,196.8)
Efavirenz	4523.9	560	123.8(113.9,134.5)
Rilpivirine	2628	272	103.5(91.9,116.6)
Atazanavir	1992.4	266	133.5(118.4,150.6)
Darunavir	2007.4	370	184.3(166.5,204.1)
Other*	627.1	87	138.7(112.4,171.2)
Total	19547	2689	137.6(132.5,142.9)

**BIC and non-contemporary regimens ("others") we not included in the antiretroviral comparisons (<100 events)*

Table S5: Sensitivity analyses for the hypertension endpoint

sensitivity analysis	variable categories	events / person-years	incidence Rate, per 1000 person-years (CI)	crude IRR (CI)	adjusted IRR (CI)	p-value	interaction statistic and *P*-value
Primary analysis (n=9,704)	INSTI with TAF	581/5700.8	101.9(94,110.5)	1.70(1.54,1.88)	1.48(1.31,1.68)	<0.001	χ^2=2.59, df=3, P=0.459
	INSTI, no TAF	1056/12514.9	84.4(79.4,89.6)	1.41(1.30,1.53)	1.25(1.13,1.39)	<0.001	
	No INSTI with TAF	205/2801.6	73.2(63.8,83.9)	1.22(1.05,1.42)	1.33(1.14,1.55)	<0.001	
	No INSTI, no TAF	1135/18975.8	59.8(56.4,63.4)	*Ref*	*Ref*		
Time-updated BMI (lagged by 12 months (n=9,704)	INSTI with TAF	581/5700.8	101.9(94,110.5)	1.70(1.54,1.88)	1.48(1.31,1.68)	<0.001	χ^2=0.98, df=3, P=0.819
	INSTI, no TAF	1056/12514.9	84.4(79.4,89.6)	1.41(1.30,1.53)	1.25(1.13,1.39)	<0.001	
	No INSTI with TAF	205/2801.6	73.2(63.8,83.9)	1.22(1.05,1.42)	1.33(1.14,1.55)	<0.001	
	No INSTI, no TAF	1135/18975.8	59.8(56.4,63.4)	*Ref*	*Ref*		
BMI increases defined as a 7 % increase in current BMI compared to pre-regimen (n=9,704)	INSTI with TAF	581/5700.8	101.9(94,110.5)	1.70(1.54,1.88)	1.48(1.31,1.68)	<0.001	χ^2=2.25, df=3, P=0.523
	INSTI, no TAF	1056/12514.9	84.4(79.4,89.6)	1.41(1.30,1.53)	1.24(1.12,1.37)	<0.001	
	No INSTI with TAF	205/2801.6	73.2(63.8,83.9)	1.22(1.05,1.42)	1.33(1.14,1.55)	<0.001	
	No INSTI, no TAF	1135/18975.8	59.8(56.4,63.4)	*Ref*	*Ref*		
EVG excluded from the INSTI group (i.e., EVG not considered INSTI) (n=9,704)	INSTI with TAF	392/2889.4	135.7(122.9,149.8)	2.26(2.02,2.54)	1.80(1.71,2.24)	<0.001	χ^2=2.16, df=3, P= 0.539
	INSTI, no TAF	968/11091.2	87.3(81.9,93)	1.46(1.34,1.58)	1.32(1.19,1.46)	<0.001	
	No INSTI with TAF	394/5613	70.2(63.6,77.5)	1.17(1.05,1.31)	1.19(1.05,1.34)	0.006	
	No INSTI, no TAF	1223/20399.5	60(56.7,63.4)	*Ref*	*Ref*		
Analysis limited to ART-experienced PLWH (n= 7,516)	INSTI with TAF	372/4193.6	88.7(80.1,98.2)	1.46(1.46,1.30)	1.41(1.28,1.71)	<0.001	χ^2=3.46, df=3, P= 0.325
	INSTI, no TAF	799/10040.7	79.6(74.2,85.3)	1.31(1.31,1.20)	1.29(1.15,1.45)	<0.001	
	No INSTI with TAF	148/2013.7	73.5(62.6,86.3)	1.21(1.21,1.02)	1.35(1.13,1.61)	0.001	
	No INSTI, no TAF	981/16195.5	60.6(56.9,64.5)	*Ref*	*Ref*		
Analysis limited to ART-naive PLWH (n= 2,188)	INSTI with TAF	209/1507.3	138.7(121.1,158.8)	2.5(2.03,3.08)	1.43(1.09,1.88)	0.009	χ^2=3.78, df=3, P= 0.287
	INSTI, no TAF	257/2474.3	103.9(91.9,117.4)	1.88(1.54,2.29)	1.35(1.07,1.71)	0.011	
	No INSTI with TAF	57/787.9	72.3(55.8,93.8)	1.31(0.96,1.77)	1.22(0.88,1.67)	0.228	
	No INSTI, no TAF	154/2780.3	55.4(47.3,64.9)	*Ref*	*Ref*		
Analysis limited to participants with controlled HIV RNA (<200 copies/mL) at baseline (n=7,103)	INSTI with TAF	356/4062.3	87.6(79,97.2)	1.42(1.26,1.61)	1.46(1.26,1.7)	<0.001	χ^2=2.35, df=3, P=0.504
	INSTI, no TAF	773/9494	81.4(75.9,87.4)	1.32(1.2,1.46)	1.33(1.18,1.49)	<0.001	
	No INSTI with TAF	148/1975.4	74.9(63.8,88)	1.22(1.02,1.45)	1.38(1.16,1.65)	<0.001	
	No INSTI, no TAF	927/15073.3	61.5(57.7,65.6)	*Ref*	*Ref*		
Follow-up censored upon switch from or to TDF/EFV (n=7292)**	INSTI with TAF	270/2370.2	113.9(101.1,128.3)	1.09(0.96,1.25)	1.12(1.06,1.31)	<0.001	χ^2=4.77, df=3, P= 0.190
	INSTI, no TAF	930/6744.9	137.9(129.3,147)	1.32(1.21,1.44)	1.21(1.10,1.46)	<0.001	
	No INSTI with TAF	25/306.6	81.5(55.1,120.7)	0.78(0.53,1.16)	1.11(0.73,1.67)	0.630	
	No INSTI, no TAF	1082/10387.7	104.2(98.1,110.6)	Ref	Ref		
Analysis limited to PLWH without prior exposure to PIs (n=4,264)	INSTI with TAF	295/2467.2	119.6(106.7,134)	2.33(2.01,2.7)	1.62(1.34,1.96)	<0.001	χ^2=0.65, df=3, P= 0.884
	INSTI, no TAF	387/4494.4	86.1(77.9,95.1)	1.68(1.46,1.93)	1.29(1.09,1.52)	0.003	
	No INSTI with TAF	101/1409.9	71.6(58.9,87.1)	1.4(1.12,1.73)	1.37(1.09,1.72)	0.006	
	No INSTI, no TAF	423/8245.7	51.3(46.6,56.4)	Ref	Ref		
Analysis limited to PLWH without prior exposure to ABC (n= 6910)	INSTI with TAF	479/4515.1	106.1(97,116)	1.86(1.66,2.08)	1.55(1.34,1.8)	<0.001	χ^2=4.48, df=3, P= 0.214
	INSTI, no TAF	628/7737.1	81.2(75.1,87.8)	1.42(1.28,1.58)	1.28(1.13,1.46)	<0.001	
	No INSTI with TAF	164/2331.3	70.3(60.4,82)	1.23(1.04,1.46)	1.29(1.09,1.54)	0.004	
	No INSTI, no TAF	789/13832.2	57(53.2,61.2)				

Note df=degrees of freedom, χ^2=chi-square. **There were few events (n=35) in PLWH receiving TAF without INSTI, and the estimates may lack precision. “INSTI with TAF” means regimen containing TAF and an INSTI, “INSTI, no TAF” means regimen containing INSTI but without TAF, “No INSTI, TAF” means regimen containing TAF but without INSTI “No INSTI, no TAF” means regimen containing without INSTI or TAF.

Table S6: Sensitivity analyses for the dyslipidemia analysis

sensitivity analysis	variable categories	events/ person-years	incidence Rate, per 1000 person-years (CI)	crude IRR (CI)	adjusted IRR (CI)	p-value	interaction *P*-value
Primary analysis (n=5,231) (Adjustment made for time-updated BMI and other confounders)	INSTI with TAF	415/2580.1	160.8(146.1,177.1)	1.24(1.10,1.40)	1.21(1.07,1.38)	<0.001	χ^2=3.64, df=3, P=0.303
	INSTI, no TAF	719/5188.4	138.6(128.8,149.1)	1.07(0.98,1.17)	1.09(0.99,1.19)	0.121	
	No INSTI with TAF	186/1184	157.1(136.0,181.4)	1.22(1.03,1.44)	1.15(0.96,1.37)	0.121	
	No INSTI, no TAF	1369/10594.5	129.2(122.5,136.3)	Ref	Ref		
Time-updated BMI (lagged by 12 months (n=5,231)	INSTI with TAF	415/2580.1	160.8(146.1,177.1)	1.24(1.10,1.40)	1.20(1.07,1.38)	<0.001	χ^2=3.21, df=3, P=0.360
	INSTI, no TAF	719/5188.4	138.6(128.8,149.1)	1.07(0.98,1.17)	1.09(0.98,1.19)	0.241	
	No INSTI with TAF	186/1184	157.1(136.0,181.4)	1.22(1.03,1.44)	1.14(0.94,1.38)	0.121	
	No INSTI, no TAF	1369/10594.5	129.2(122.5,136.3)	Ref	Ref		
BMI increase defined as a 7 % increase in BMI compared to the last BMI before starting the current ART (N=5,231)	INSTI with TAF	415/2580.1	160.8(146.1,177.1)	1.24(1.10,1.40)	1.22(1.07,1.39)	<0.001	χ^2=3.51, df=3, P=0.319
	INSTI, no TAF	719/5188.4	138.6(128.8,149.1)	1.07(0.98,1.17)	1.05(0.98,1.16)	0.256	
	No INSTI with TAF	186/1184	157.1(136.0,181.4)	1.22(1.03,1.44)	1.16(0.94,1.36)	0.301	
	No INSTI, no TAF	1369/10594.5	129.2(122.5,136.3)	Ref	Ref		
EVG excluded from the INSTI group (i.e., EVG not considered INSTI) (n=5,231)	INSTI with TAF	347/1614.7	214.9(195.3,236.7)	1.63(1.48,1.98)	1.41(1.21,1.64)	<0.001	χ^2=2.99, df=3, P= 393
	INSTI, no TAF	602/5078.1	118.5(110.1,127.5)	0.90(0.81,1.13)	1.04(0.82,1.21)	0.123	
	No INSTI with TAF	208/1213	171.5(148.5,198.0)	1.30(1.10,1.46)	1.21(1.05,1.36)	0.021	
	No INSTI, no TAF	1532/11641.2	131.6(124.8,138.8)		Ref		
Analysis limited to ART-experienced PLWH (n= 3902)	INSTI with TAF	315/1924.7	163.7(148.7,180.2)	1.27(1.13,1.43)	1.21(1.10,1.38)	<0.001	χ^2=5.86, df=3, P=0.143
	INSTI, no TAF	539/3870.5	139.3(129.4,149.8)	1.07 (0.97,1.18)	1.05 (0.93,1.15)	0.129	
	No INSTI with TAF	130/883.2	147.2(127.4,170.0)	1.14(0.96,1.36)	1.14(0.97,1.42)	0.069	
	No INSTI, no TAF	1021/7903.3	129.2(122.5,136.3)	Ref	Ref		
Analysis limited to ART-naive PLWH (n= 1,329)	INSTI with TAF	100/655.5	152.6(138.6,168.0)	1.18(1.12.,1.33)	1.17(1.14.,1.36)	<0.001	χ^2=3.66, df=3, P= 0.301
	INSTI, no TAF	180/1318.2	136.5(126.9,146.9)	1.05(0.96,1.14)	1.05(0.97,1.14)	0.121	
	No INSTI with TAF	56/300.8	186.2(161.2,215.0)	1.44(1.21,1.68)	1.20(1.22,1.69)	0.001	
	No INSTI, no TAF	348/2691.7	129.3(122.6,136.4)	Ref	Ref		
Analysis limited to participants with controlled HIV RNA (<200 copies/mL) at baseline (n= 3769)	INSTI with TAF	299/1790.6	167.0(149.9,189.7)	1.32(1.16,1.48)	1.25(1.10,1.36)	<0.001	χ^2=6.23, df=3, P=0.101
	INSTI, no TAF	667/4858.4	137.3(127.8,145.6)	1.09(0.99,1.21)	1.04(0.89,1.18)	0.121	
	No INSTI with TAF	156/1050.6	148.5(124.4,174.5)	1.18(0.97,1.42)	1.16(1.06,1.39)	0.048	
	No INSTI, no TAF	1344/10689.5	125.7(118.4,132.9)	Ref	Ref		
Dyslipidemia defined without triglycerides (6364)	INSTI with TAF	368/1901.3	193.6(174.3,214.8)	1.37(1.21,1.54)	1.25(1.15,1.42)	<0.001	χ^2=6.61, df=3, P=0.085
	INSTI, no TAF	788/5183.6	152.0(141.9,163.4)	1.08(0.99,1.18)	1.07(0.99,1.18)	0.062	
	No INSTI with TAF	161/963.2	167.2(140.9,194.9)	1.18(0.98,1.40)	1.18(1.04,1.40)	0.041	
	No INSTI, no TAF	1643/11653.1	141.0(134.5,149.8)	Ref	Ref		
Follow-up censored upon switch from or to TDF/EFV (n=3232) **	INSTI with TAF	204/1001.1	203.8(178.2,234.2)	1.27(1.09,1.47)	1.22(1.01,1.33)	0.032	χ^2=4.19, df=3 P= 0.363
	INSTI, no TAF	346/2459.6	140.7(126.2,153.2)	0.87(0.75,1.00)	0.76(0.56,1.11)	0.186	
	No INSTI with TAF	36/166.1	216.7(152.9,289.1)	1.34(0.91,1.78)	1.18(0.88,1.88)	0.423	
	No INSTI, no TAF	999/6181.7	161.6(150.6,170.2)	Ref	Ref		
Analysis limited to PLWH without prior exposure to PIs at baseline (n=3975)	INSTI with TAF	232/976.8	237.5(209.4,269.4)	1.63(1.38,1.91)	1.35(1.16,1.61)	<0.001	χ^2=5.69, df=3 P= 0.128
	INSTI, no TAF	400/2179.9	183.5(167.2,202.4)	1.26(1.08,1.37)	1.22(1.06,1.38)	0.002	
	No INSTI with TAF	97/550.6	176.1(144.0,219.1)	1.21(0.95,1.43)	1.26(1.03,1.69)	0.016	
	No INSTI, no TAF	763/5246.8	145.4(132.2,154.1)	Ref	Ref		
Analysis limited to PLWH without prior exposure to ABC at baseline (n=4,591)	INSTI with TAF	302/1599	188.9(170.2,209.1)	1.41(1.26,1.63)	1.34(1.18,1.49)	<0.001	χ^2=6.11, df=3 P= 0.106
	INSTI, no TAF	567/3425.1	165.5(149.6,182.6)	1.23(1.14,1.39)	1.18(1.07,1.31)	0.019	
	No INSTI with TAF	139/807.2	172.2(148.3,201.2)	1.29(1.09,1.56)	1.26(1.06,1.54)	0.019	
	No INSTI, no TAF	1140/8532.7	133.4(126.1,139.4)	Ref	Ref		

Note df=degrees of freedom, χ^2=chi-square. **There were few events (n=35) in PLWH receiving TAF without INSTI, and the estimates may lack precision. "INSTI with TAF" means regimen containing TAF and an INSTI, "INSTI, no TAF" means regimen containing INSTI but without TAF, "No INSTI, TAF" means regimen containing TAF but without INSTI "No INSTI, no TAF" means regimen containing without INSTI or TAF.