Published in final edited form as:

Lancet HIV. 2024 May ; 11(5): e321–e332. doi:10.1016/S2352-3018(23)00328-4.

Association between change in body mass index and risk of hypertension and dyslipidemia in people receiving integrase inhibitors and/or tenofovir alafenamide compared to other contemporary antiretroviral regimens: the RESPOND consortium of prospective cohorts

Dathan M. Byonanebye, PhD[1,2], **Prof. Mark N. Polizzotto, PhD**[3], **Fernando Maltez, PhD**[4], **Andri Rauch, PhD**[5], **Katharina Grabmeier-Pfistershammer, MD**[6], **Ferdinand Wit, PhD**[7], **Prof. Stéphane De Wit, PhD**[8], **Prof. Antonella Castagna, MD**[9], **Prof. Antonella D'Arminio Monforte, MD**[11], **Prof. Cristina Mussini, MD**[12], **Jan-Christian Wasmuth, MD**[13], **Eric Fontas, PhD**[14], **Irene Abela, PhD**[15,16], **Mario Sarcletti, MD**[17], **Loveleen Bansi-Matharu, PhD**[18], **Nadine Jaschinski, MD**[19], **Lars Peters, DMSc**[19], **Sean R Hosein**[20], **Vani Vannappagari, PhD**[21], **Cal Cohen, MD**[22], **Emiliano Bissio, MD**[23], **Prof. Amanda Mocroft, PhD**[18,19], **Prof. Matthew Law, PhD**[1], **Lene Ryom, PhD**[19], **Prof. Kathy Petoumenos, PhD**[1,*] **RESPOND study group**

[1]Kirby Institute, University of New South Wales, New South Wales, Australia

[2]School of Public Health, Makerere University, Kampala, Uganda

[3]The Australian National University, Canberra, Australia

[4]Hospital Curry Cabral, Lisbon, Portugal

[5]Department of Infectious Diseases, Inselspital, Bern University Hospital, Bern 3010, Switzerland

[6]Medizinische Universität Wien, Vienna, Austria

Corresponding Author and Address: Dathan M. Byonanebye, Makerere University School of Public Health, P.O Box 7062, Kampala, Uganda, dbyonanebye@musph.ac.ug. **Alternative corresponding Author and Address:** Kathy Petoumenos, Biostatistics and Databases Program, Kirby Institute, University of New South Wales, Level 6, Wallace Wurth Building, UNSW Sydney, NSW 2052, Kpetoumenos@kirby.unsw.edu.au.

*The study Group team members are listed in the appendix.

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. KP and ML accessed and verified the data. Finally, all authors approved and had responsibility for the decision to submit for publication.

Conflict of interest

AM has received travel support, lecture, 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 and have stocks from the respective companies. ML has received sitting fees from Certa Therapeutics DSMB, and KG has served on advisory boards and provided lectures for Gilead Sciences and ViiV. AR has received support for attending meetings and travel from Gilead Sciences and Pfizer, received an investigator-initiated trial grant from Gilead Sciences and participated on a Data Safety Monitoring Board or Advisory Board for MSD and Pfizer. All remuneration went to AR's institution and not to AR personally. The rest of the authors have declared no conflict of interest.

[7]Stichting HIV Monitoring (SHM), Amsterdam, The Netherlands

[8]Department of Infectious Diseases, St Pierre University Hospital Bruxelles, Université Libre de Bruxelles, Brussels, Belgium

[9]San Raffaele Scientific Institute, Università Vita-Salute San Raffaele, Milano, Italy

[11]ASST Santi Paolo e Carlo, Milan, Italy

[12]Università degli Studi di Modena, Modena, Italy

[13]University Hospital Bonn, Bonn, Germany

[14]Nice HIV cohort, Université Côte d'Azur et Centre Hospitalier Universitaire, Nice, France.

[15]University of Zurich, Zurich, Switzerland

[16]University Hospital of Zurich, Zurich, Switzerland

[17]Department of Dermatology, Venerology and Allergology, Medical University Innsbruck, Innsbruck, Austria

[18]Center for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, University College London, London, UK

[19]CHIP, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

[20]European AIDS Treatment Group, Belgium

[21]ViiV Healthcare, RTP, North Carolina, USA

[22]Gilead Sciences, Foster City, California, USA

[23]Merck Sharp & Dohme, Madrid, Spain.

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 contemporary regimens.

Methods: The study analyzed prospective data from RESPOND, an international consortium of observational HIV cohorts in Europe and Australia. Participants were eligible if they were ≥18 years, receiving INSTI-containing antiretroviral regimens (ART) or contemporary non-INSTI, with baseline and ≥2 follow-up BMI and lipid/blood pressure measurements, and 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 people receiving INSTIs and/or TAF and test for interaction between time-updated antiretroviral therapy (ART) regimen and BMI.

Results: 9704 and 5231 participants were included in hypertension and dyslipidemia analyses, respectively. In the univariable model, hypertension was more common in individuals receiving INSTI with TAF (IRR 1·70, 95% confidence intervals [CI] 1·54–1·88) or INSTI without TAF (IRR 1·41, 95% CI1·30–1·53), compared to those receiving neither INSTI nor TAF. Adjustment for time-updated BMI and confounders attenuated risk in participants receiving INSTI with (IRR

1·48, 95% CI 1·31–1·68) or without TAF (IRR 1·25, 1·13–1·39). Similarly, dyslipidemia was more common in participants using TAF with INSTI (IRR 1·24, 1·10–1·40) and TAF alone (IRR 1·22, 95% CI 1·03–1·44). Adjustment for BMI and confounders attenuated the risk in participants receiving TAF with INSTI (IRR 1·21, 95% CI 1·07–1·37), while the risk in those receiving TAF alone (IRR 1·15, 95% CI 0·96–1·38) became non-significant. Hypertension and dyslipidemia increased equally with increasing BMI between regimens (*P*-interaction=0·46 and 0·31, respectively).

Conclusion: Although residual confounding cannot be entirely excluded, the use of INSTIs was associated with incident hypertension and TAF with dyslipidemia, and the association was partially mediated by weight gain. These results reiterate the need for hypertension screening in PLWH.

Funding: RESPOND is financially supported by ViiV Healthcare, Merck Life Sciences, Gilead Sciences, CHIP and the AHOD cohort by grant No. U01-AI069907 from the U.S. National Institutes of Health, and GNT2023845 of the National Health and Medical Research Council, Australia. Additional support has been provided by participating cohorts (listed in the appendix) by contributing data and/or statistical support.

Keywords

Hypertension; Dyslipidemia; Weight gain; Integrase Inhibitors; Tenofovir Alafenamide

INTRODUCTION

By June 2021, approximately 22 million people living with HIV 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]. The extent and severity of INSTI-associated weight gain vary for individual antiretroviral drugs within the class, with a higher risk associated with dolutegravir (DTG), bictegravir (BIC), and raltegravir (RAL) than with elvitegravir (EVG)[2,3]. 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[2,4].

Similar to the general population, weight gain in people with HIV is associated with hypertension[5], diabetes mellitus[6], dyslipidemia[7], and obesity with cardiovascular disease[8]. Analyses in some randomized control trials (RCTs)[9,10] and cohorts[11–15] have reported increases in blood pressure (BP) or incident hypertension following the initiation of INSTIs. Relatedly, in an analysis of a South African cohort, participants who switched from efavirenz (EFV) to DTG gained more weight and had an increased risk of hypertension compared to those remaining on EFV[16]. We also recently reported a higher incidence of hypertension in people receiving INSTIs compared to non-nucleoside reverse transcriptase inhibitors (NNRTIs)[15]. The evidence linking INSTI use with dyslipidemia is inconsistent, with some studies reporting neutral effects[17,18] and others reporting weight-related increases in lipid levels[19,20]. In contrast, the evidence linking TAF use to increases in lipid levels is stronger[18,21].

It remains unclear whether people 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 people 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 participants in Europe and Australia. The details of cohort membership and data collection procedures have been previously reported[18]. 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. Participants in RESPOND received stable ART regimens with median time of 6(4–7) years before switching ART class.

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 an NNRTI (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 hypertension and dyslipidemia, assessed separately. Consistent with prior RESPOND analyses[15], 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, consistent with our prior analysis[18].

Statistical analysis

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]. The covariates closest to the baseline date 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/1·73m^2 [without race adjustment] at least 90 days apart. Where data was missing, a “missing” category was assigned, and variables were fitted as categorical variables. We did not impute missing data as the missingness of data on some variables is not random in some cases. For example, some countries prohibit collecting data on ethnicity and sex orientation. A similar approach has been used in other analyses in DAD and RESPOND.

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. Data were tested for overdispersion, and multivariable Poisson regression was used to determine the IRRs of hypertension and dyslipidemia in individuals 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[26], 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 participants 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 $P<0{\cdot}05$. Data were prepared using SAS Enterprise Guide version 8.3 (SAS Institute Inc., Cary, NC, USA) and analysed with Stata version 17.0 (StataCorp, College Station, Texas, USA).

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[2], since EVG has not been associated with weight gain like other INSTIs[2], 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.

Ethics approval and patient consent

Participants are consented to share data with RESPOND according to local requirements. Participants are pseudonymised at enrolment by assigning a unique identifier by the participating cohort before data transfer to RESPOND. According to national or local requirements, all cohorts have approval to share data with RESPOND. Ethical approvals are obtained, if required, from the relevant bodies for collection and sharing of data. Data are stored on secure servers at the RESPOND coordinating centre in Copenhagen, Denmark, in accordance with current legislation and under approval by The Danish Data Protection Agency (approval number 2012–58-0004, RH-2018–15, 26/1/2018), under the EU General Data Protection Regulation (2016/679).

Role of the funding source

As per RESPOND governance, funders of the study were also academic collaborators, and employees or associates could be included as co-authors if they met the International Committee of Medical Journal Editors criteria. However, funding bodies (including employees and associates hereof) were not in a position to veto study design, data collection, data analysis, data interpretation, or writing of the manuscript. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the listed institutions or funders.

RESULTS

Of the 35941 participants in RESPOND, 13356 (37·2%) participants had baseline BMI and BP results and ≥2 follow-up measurements, 3652 (27·3%) of whom had hypertension and were excluded (Appendix page 2). The characteristics of participants excluded from the analysis (including those with hypertension at baseline) are shown in Appendix page 14 and 18. 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 (Appendix page 8).

A total of 28941 RESPOND participants received 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 (Appendix page 3). The characteristics of participants excluded from the analysis (including those with dyslipidemia at baseline) are shown in Appendix page 15 and 20. 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 (Appendix page 10).

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). The overall median [IQR] follow-up was 3.9 (1.7,6.1) years, while the follow-up periods on specific regimens were 2.0 (0.9,3.3) for INSTI with TAF, 2.2 (0.9,3.9) for INSTI without-TAF, 3.7 (1.5,5.9) for TAF without INSTI, and 2.0 (1.0, 2.9) for participants receiving regimens without INSTI or TAF. 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 individuals receiving INSTIs with TAF (102 per 1000 person-years, 95% CI 94–111) and those without TAF (184 per 1000 person-years, 95% CI 79–90) or TAF without INSTIs (73 per 1000 person-years, 95% CI 64–84) than in those receiving regimens without TAF or INSTIs (60 per 1000 person-years, 95% CI 57–64) (Figure 1).

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). The overall median [IQR] follow-up was 3.2 (1.2,5.8) years, while the follow-up periods on the regimens were 1.8 (0.8,3.3) for INSTI with TAF, 2.0 (0.7,3.8) for INSTI without-TAF, 2.8 (1.0,5.5) for TAF without INSTI, and 2.1 (1.0, 3.2) for participants receiving regimens without INSTI or TAF. 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, 95% CI 146–177) and in those receiving TAF without INSTIs (157, 95% CI 136–181) than in those receiving INSTI without TAF (139, 95% CI 129–149) or ART regimens without TAF or INSTIs (129, 95% CI 122–136) (Figure 1).

In the univariable model, hypertension was more common in individuals receiving INSTI with TAF (IRR 1·70, 95% CI 1·54–1·88) or without TAF (1·41, 95% 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 individuals receiving INSTI with TAF (adjusted incidence rate ratio

(aIRR) 1·56, 95% CI 1·38–1·77) or without TAF (1·29, 95% CI 1·17–1·43), 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 participants receiving INSTI with TAF (1·48, 95% CI 1·31–1·68) or without TAF (1·25, 95% CI 1·13–1·39) (Figure 2). The risk of hypertension was consistently higher in individuals receiving INSTI with TAF across all BMI quintiles (Appendix page 4). The association between ART regimens and hypertension was not different by sex (*P*-interaction=0·12). Overall, the risk of hypertension increased with increasing time-updated BMI, and the association was not different in participants receiving different ART combinations (*P*-interaction=0·46) (Appendix page 12).

In the univariate model, dyslipidemia was 24% (IRR 1·24, 95% CI 1·10–1·40) and 22% (IRR 1·22, 95% CI 1·03–1·44) more common in individuals 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 participants currently receiving TAF with INSTI (aIRR 1·22, 95% CI 1·08–1·38) or without INSTI (1·19, 95% 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 participants currently receiving TAF and INSTI (1·21, 95% 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, 95% 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 individuals receiving TAF compared to non-TAF regimens across all BMI quintiles (Appendix page 6). The association between ART regimens and dyslipidemia did not differ by sex (*P*-interaction=0·29). Additionally, the risk of dyslipidemia increased with increasing time-updated BMI, and the association did not differ by ART regimens (*P*-interaction=0·30) (Appendix page 13).

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 (Appendix page 11). In a multivariable model adjusted for time-updated BMI, NRTI backbone, and other confounders, the incidence of hypertension was higher in individuals 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[2]. The association between changes in BMI and hypertension did not differ by individual antiretrovirals (*P*-interaction=0·36).

In a full model adjusted for time-updated BMI, NRTI backbone, and other confounders, the incidence of dyslipidemia was higher in individuals 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[18]. The association between dyslipidemia and changes in BMI did not statistically differ between individual antiretrovirals (*P*-interaction=0·19).

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 the ART regimens (Appendix page 12 and 13).

DISCUSSION

This study examined the risk of hypertension and dyslipidemia in people 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, and that the risk differs by individual antiretroviral drugs, similar to what was shown for other classes[25]. The risk of hypertension and dyslipidemia in participants receiving INSTI and/or TAF was attenuated but remained significant even after adjustment for time-updated BMI, suggesting that weight gain may play a mechanistic role. 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.

Overall, the results are consistent with previous results that reported an association between exposure to INSTIs and increased BP or incident hypertension (Appendix page 16) and emphasize the need for hypertension and dyslipidemia monitoring in all people living with HIV, especially those who gain weight. In the ADVANCE trial, incident hypertension was more common in PLWH receiving DTG-containing regimens than in those receiving EFV, but 95% of incident hypertension cases were treated, and there was no difference in mean SBP and hypertension between DTG and EFV arms, including when DTG and TAF were used simultaneously, at 192 weeks[9]. Therefore, hypertension screening and treatment can be successfully integrated into HIV care, including in resource-limited settings. Finally, while these results suggest that weight gain may contribute to INSTI-associated risk, it is unclear whether other mechanisms, such as activation of the neuroendocrine and renin-angiotensin-aldosterone systems and derangement in the lipoid system, which have been described for some antiretroviral agents[27], have a contributing role. Therefore, in the absence of a clear causal relationship, INSTIs should remain the preferred ART option due to their better tolerability, virologic efficacy, high resistance barrier, and the emerging evidence on successful treatment of incident hypertension[9].

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[21]. 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[28] 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[18,21]. 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[17]. However, some studies

have reported an increase in lipid levels in people experiencing INSTI-associated weight gain[19], 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[18].

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). Furthermore, there may be potential channeling bias with participants at high cardiovascular risk being preferentially initiated on INSTI-based regimens. However, we compared participants 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. Finally, while BMI is associated with hypertension and dyslipidemia, it has limitations as an indicator of obesity and a risk factor for cardiovascular disease compared to other anthropometric measures. Despite the limitations, the analysis provides a signal based on routinely collected clinic-based data 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 that have linked INSTIs with increased cardiovascular risk[29,30], further research is warranted to fully understand the associations between the use of INSTI and TAF, weight gain, and cardiovascular risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The AIDS Therapy Evaluation in the Netherlands Cohort (ATHENA), The Australian HIV Observational Database (AHOD), Austrian HIV Cohort Study (AHIVCOS), Brighton HIV cohort, CHU Saint-Pierre, Croatian HIV cohort, EuroSIDA Cohort, Frankfurt HIV Cohort Study, Georgian National AIDS Health Information System (AIDS HIS), Italian Cohort Naive Antiretrovirals (ICONA), Modena HIV Cohort, Nice HIV Cohort, PISCIS Cohort Study, Royal Free Hospital Cohort, San Raffaele Scientific Institute,- Swedish InfCare HIV Cohort, Swiss HIV Cohort

Study (SHCS), University Hospital Bonn, and University Hospital Cologne. The details of the RESPOND study group can be found online and is listed in the appendix (Appendix pages 22–23). RESPOND is further financially supported by ViiV Healthcare, Merck Life Sciences, Gilead Sciences, the EuroSIDA Cohort and the AHOD cohort by grant No. U01-AI069907 from the U.S. National Institutes of Health, and GNT1050874 of the National Health and Medical Research Council, Australia.

Data sharing section

The RESPOND Scientific Steering Committee (SSC) encourages the submission of concepts for research projects. Online research concepts should be submitted to the RESPOND secretariat (respond. rigshospitalet@regionh.dk); for guidelines on how to submit research concepts see the RESPOND governance and procedures point 6. The secretariat will direct the proposal to the relevant Scientific Interest Group, where the proposal will initially be discussed for scientific relevance before being submitted to the SSC for review. Once submitted to the SSC, the research concept's scientific relevance, relevance to RESPOND's ongoing scientific agenda, design, statistical power, feasibility, and overlap with already approved projects will be assessed. Upon completion of the review, feedback will be provided to the proposer or proposers. In some circumstances, a revision of the concept might be requested. If the concept is approved for implementation, a writing group will be established consisting of the proposers (up to seven people who were centrally involved in developing the concept), representatives from RESPOND cohorts, and representatives from the Statistical Department and Coordinating Center. All individuals involved in the process of reviewing these research concepts are bound by confidentiality. All data within RESPOND from individual cohorts are de-identified. The present RESPOND data structure and a list of all collected variables and their definition can be found online. For any inquiries regarding data sharing, please contact the RESPOND secretariat (respond.rigshospitalet@regionh.dk).

REFERENCES

1. World Health Organization. Update on the transition to dolutegravir-based antiretroviral therapy: report of a WHO meeting, 29–30 March 2022. 2022 https://www.who.int/publications/i/item/9789240053335.
2. 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: e711–22. [PubMed: 34555326]
3. 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. DOI:10.1186/S12879-022-07091-1.
4. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. New England Journal of Medicine 2019. DOI:10.1056/nejmoa1902824.
5. 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: 403–7. [PubMed: 25979413]
6. 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: 2107–19. [PubMed: 35848573]
7. 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. DOI:10.1093/ofid/ofz491.

8. 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: 255–68. [PubMed: 26216031]
9. Venter F, Sokhela S, Bosch B, et al. Risks of hypertension with first-line dolutegravir (DTG) and tenofovir alafenamide (TAF) in the NAMSAL and ADVANCE trials. In: 12th International AIDS Society Conference on HIV Science. Brisbane: IAS, 2023. https://programme.ias2023.org/Abstract/Abstract/?abstractid=5640 (accessed Sept 8, 2023).
10. Petoumenos K, Nyein PP, Borok M, et al. Associations between antiretroviral regimen and changes in blood pressure: results from the D2EFT study. In: 12th International AIDS Society Conference on HIV Science (IAS 2023). Brisbane: IAS, 2023. https://www.iasociety.org/sites/default/files/IAS2023/abstract-book/IAS_2023__Abstracts.pdf (accessed Sept 12, 2023).
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. DOI:10.1097/QAI.0000000000002447.
12. 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. [PubMed: 34176240]
13. 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. [PubMed: 36465432]
14. 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. DOI:10.2139/ssrn.4251322.
15. 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.
16. 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. DOI:10.2139/ssrn.4251322.
17. 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. DOI:10.1186/s12879-019-3975-6.
18. 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: 869–82. [PubMed: 33443370]
19. Rizzardo S, Lanzafame M, Lattuada E, et al. Dolutegravir monotherapy and body weight gain in antiretroviral naïve patients. AIDS. 2019; 33: 1673–4. [PubMed: 31305333]
20. 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. https://journals.lww.com/jaids/Fulltext/2023/01010/Weight_Gain_and_Metabolic_Effects_in_Persons_With.9.aspx.
21. 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: 758–67. [PubMed: 33721521]
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. [PubMed: 30174450]
23. 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. [PubMed: 27114439]
24. 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. [PubMed: 30450860]

25. 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: 605–18. [PubMed: 30019813]

26. Francois Venter WD, Sokhela S, Calmy A, et al. Weight gain stopping/switch rules for antiretroviral clinical trials. AIDS 2021; 35: S183–8. [PubMed: 34848585]

27. Fahme SA, Bloomfield GS, Peck R. Hypertension in HIV-Infected Adults. Hypertension 2018. DOI:10.1161/hypertensionaha.118.10893.

28. 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: 559–66.

29. 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; published online June. DOI:10.1016/S2352-3018(22)00094-7.

30. Rebeiro PF, Emond B, Rossi C, et al. Incidence of cardiometabolic outcomes among people living with HIV-1 initiated on integrase strand transfer inhibitor versus non-integrase strand transfer inhibitor antiretroviral therapies: a retrospective analysis of insurance claims in the United States. J Int AIDS Soc 2023; 26: e26123. [PubMed: 37306118]

RESEARCH IN CONTEXT

Evidence before this study

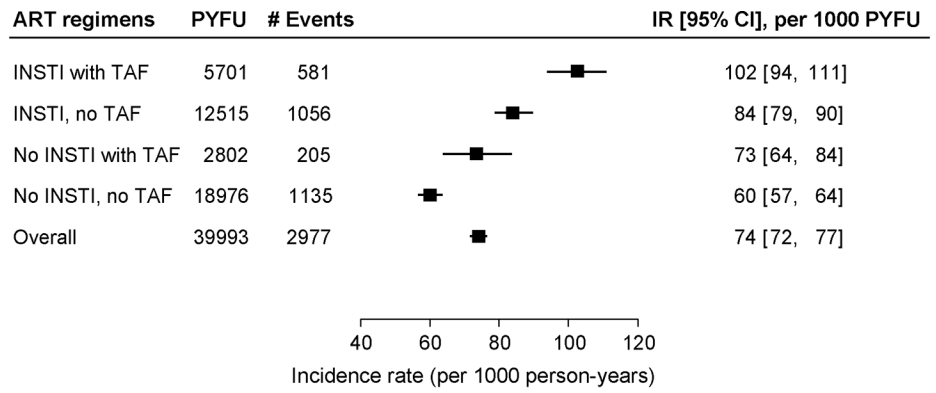
We searched MEDLINE, Embase, Google Scholar, and Web of Science for randomized control trials (RCTs) or cohorts published before 31 August 2023. We used free-text or Medical Subject Headings (MeSH) terms: “tenofovir alafenamide” or “integrase Inhibitors” and “body weight changes” and “dyslipidemia”, “hypertension”, “blood pressure”, or “lipids”. The literature search revealed that the use of integrase inhibitors (INSTIs) and tenofovir alafenamide (TAF) is associated with weight gain, and the simultaneous use increases the risk and severity of weight gain. Data from some cohorts and randomized controlled trials have reported an association between INSTIs and hypertension, but this signal has not been validated in large and clinically heterogeneous cohorts. Furthermore, it was unclear from the available literature whether weight gain explains the association between INSTIs and hypertension and TAF with dyslipidemia and whether INSTI and TAF-associated weight gain confers a higher risk of these weight-related clinical events.

Added value of this study

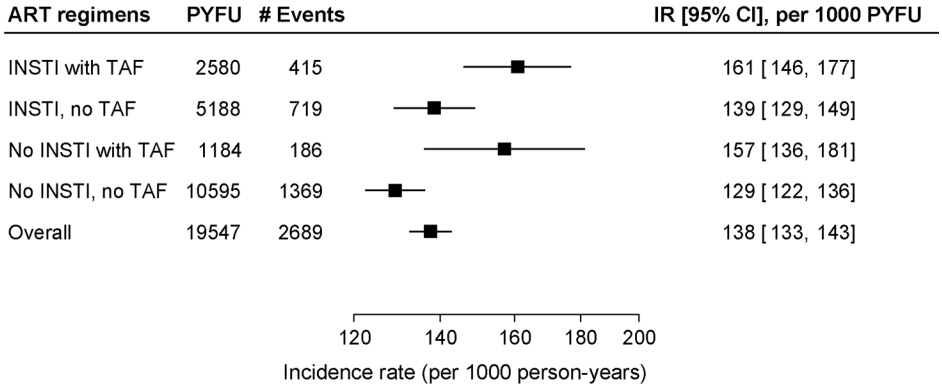
In this analysis, we explored three key issues: whether current use of INSTI and/or TAF is associated with incident hypertension and dyslipidemia; whether changes in body mass index (BMI) mediate the risk; and whether BMI changes differentially increase the risk of hypertension and dyslipidemia in PLWH receiving INSTIs and/or TAF compared to individuals receiving regimens without INSTI/TAF. To explore the impact of weight gain on these findings, we adjusted for time-updated BMI (i.e., BMI changed over follow-up time) in the analyses. In our analysis, the use of INSTI was associated with incident hypertension, while the use of TAF was associated with dyslipidemia. Adjusting for time-updated BMI attenuated the association between INSTI and hypertension, while the association between TAF and dyslipidemia was no longer statistically significant. Our results show that weight gain is associated with an increased risk of hypertension and dyslipidemia, regardless of the antiretroviral therapy (ART) regimen.

Implications of all the available evidence

With the increasing adoption of INSTIs as first-line regimens, our analysis highlights the need for hypertension and dyslipidemia screening, especially in settings with limited resources for routine monitoring of all PLWH. Furthermore, people receiving ART, especially regimens associated with weight gain, should receive lifestyle and behavioral interventions to reduce weight gain. The association between the use of INSTI and incident hypertension, including the underlying mechanisms, should be further investigated in RCTs with extended follow-up.



Panel A: Incidence rates of hypertension by ART regimen (time-updated)



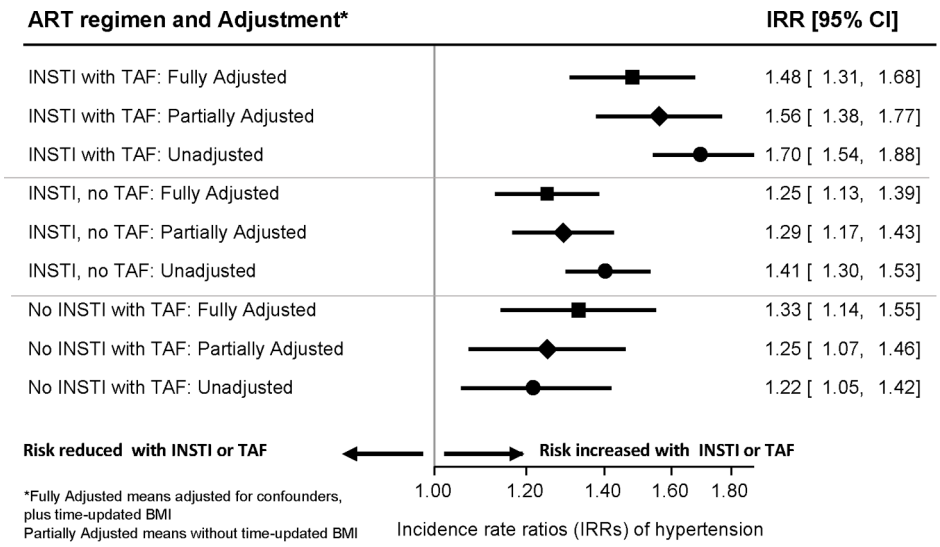
Panel B: Incidence rates of dyslipidaemia by ART regimen (time-updated)

Figure 1: Unadjusted incidence rates of hypertension (panel A) and dyslipidemia (panel B) in people currently receiving combinations of INSTI and TAF versus regimens without INSTI or TAF

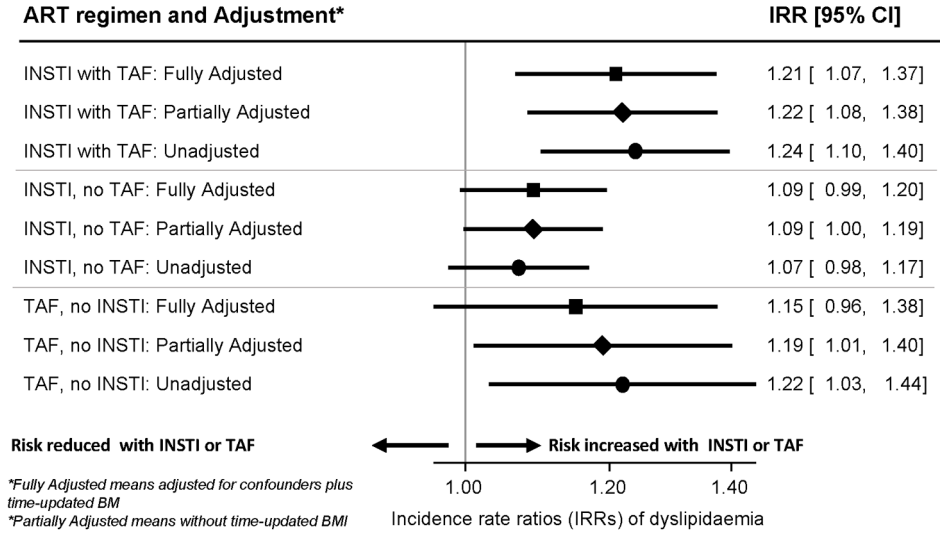
1. TAF-tenofovir alafenamide, INSTI-integrase strand transfer inhibitors, ART-antiretroviral therapy, IR-incidence rates (per 1000 person-years).

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*:



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



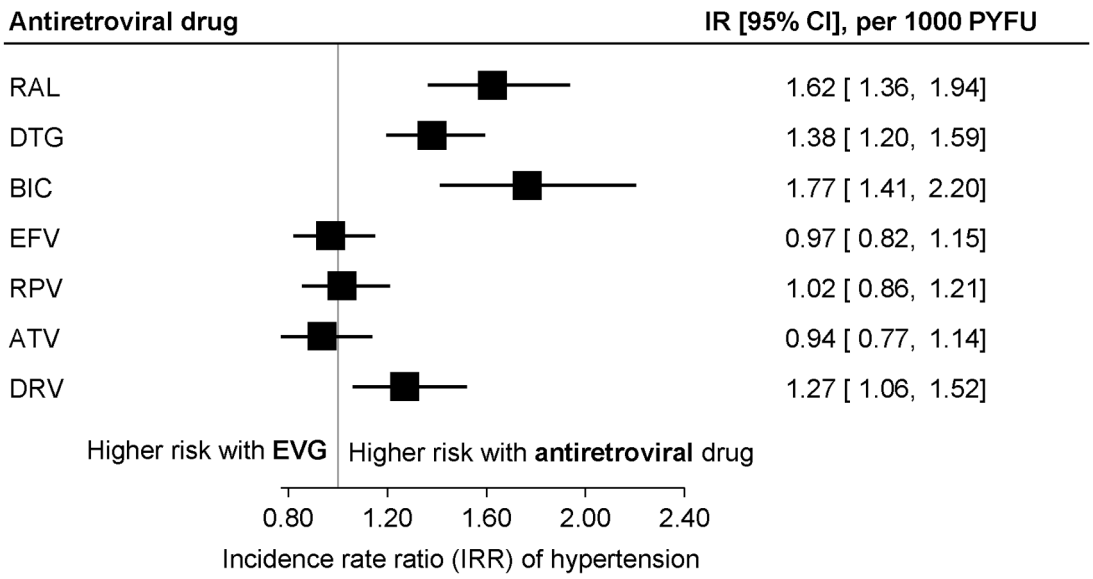
Panel B: Adjusted and unadjusted IRRs of dyslipidemia in people with HIV receiving combinations of INSTI with TAF versus those receiving contemporary regimens without INSTI or TAF.

Figure 2: Adjusted and unadjusted incident rate ratios (IRRs) of hypertension (panel A) and dyslipidemia (panel B) in participants currently receiving combinations of INSTI with TAF.

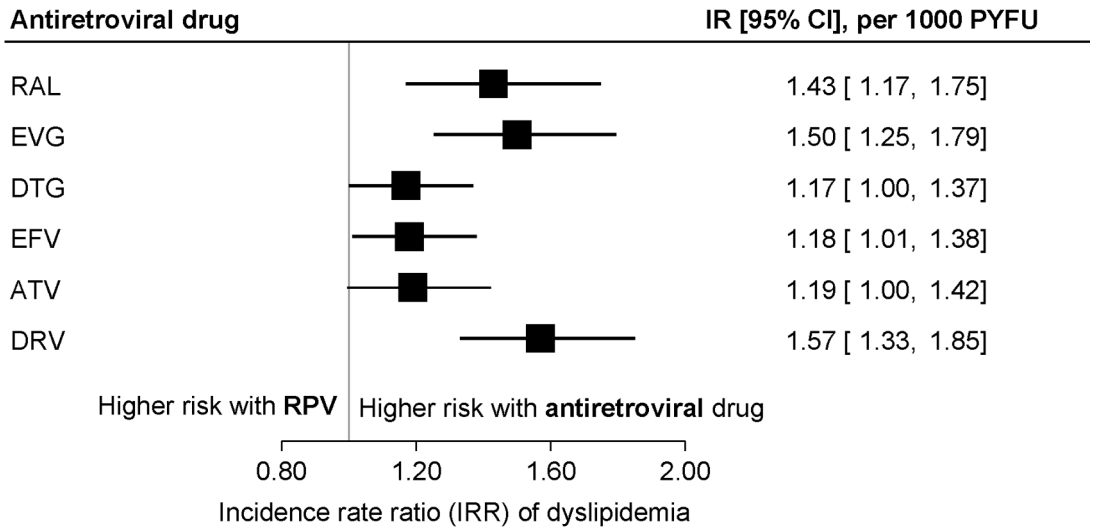
1. TAF-tenofovir alafenamide, INSTI-integrase strand transfer inhibitors, ART-antiretroviral therapy, IR-incidence rates (per 1000 person-years).

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*



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



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

Figure 3: Adjusted incident rate ratios of hypertension (panel A) and dyslipidemia (panel B) in participants receiving individual antiretrovirals.

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*.

Table 1:

Baseline characteristics of participants with versus those without incident hypertension

Variable†	No incident hypertension (n=6727)	Incident Hypertension (n=2,977)	Total (n=9,704)
Gender			
Female	1771(26·3)	606(20·4)	2377(24·5)
Male	4956(73·7)	2371(79·6)	7327(75·5)
Ethnicity ▫			
White	4673(69·5)	2280(76·6)	6953(71·7)
Black	548(8·2)	276(9·3)	824(8·5)
Other/Unknown	1506(22·4)	421(14·1)	1927(19·9)
Region			
W.Europe	3313(49·3)	1890(63·5)	5203(53·6)
S.Europe	700(10·4)	140(4·7)	840(8·7)
N. Europe*	2714(40·3)	947(31·8)	3661(37·7)
Route of HIV acquisition			
MSM	3240(48·2)	1511(50·8)	4751(49·0)
IDU	894(13·3)	326(11·0)	1220(12·6)
Heterosexual	2243(33·3)	987(33·2)	3230(33·3)
Other/Unknown	350(5·2)	153(5·1)	503(5·2)
ART Status			
Naive	1511(22·5)	677(22·7)	2188(22·6)
Experienced	5216(77·5)	2300(77·3)	7516(77·5)
Prior AIDS			
Yes	1284(19·1)	687(23·1)	1971(20·3)
No	5443(80·9)	2290(76·9)	7733(79·7)
Hepatitis B infection			
Positive	357(5·3)	147(4·9)	504(5·2)
Negative	5796(86·2)	2578(86·6)	8374(86·3)
Unknown	574(8·5)	252(8·5)	826(8·5)
Hepatitis C infection			
Positive	1453(21·6)	551(18·5)	2004(20·7)
Negative	4272(63·5)	1943(65·3)	6215(64·1)
Unknown	1002(14·9)	483(16·2)	1485(15·3)
Smoking Status			
Current	2266(33·7)	1009(33·9)	3275(33·8)
Previous	822(12·2)	394(13·2)	1216(12·5)
Never	2422(36·0)	1054(35·4)	3476(35·8)
Unknown	1217(18·1)	520(17·5)	1737(17·9)
Chronic Kidney Disease			

Variable†	No incident hypertension (n=6727)	Incident Hypertension (n=2,977)	Total (n=9,704)
Yes	411(6·1)	361(12·1)	772(8·0)
No	6287(93·5)	2612(87·7)	8899(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	6203(92·2)	2729(91·7)	8932(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)	2837(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)	2833(95·2)	9371(96·6)
Age (years)	43(35,50)	47(39,54)	44(36,51)
Number missing	0(0)	0(0)	0(0)
Baseline CD4 (cells per μL)	548(368,744)	535(364,723)	544(367,739)
Number missing	0(0)	0(0)	0(0)
Nadir CD4 (cells per μL)	254(132,391)	228(110,356)	246(125,379)
Number missing	0(0)	0(0)	0(0)
Baseline HIV RNA (copies per mL)	39(19,408)	39(19,268)	39(19,367)
Number missin	0(0)	0(0)	0(0)
Baseline BMI (kg/m2)	23·1(21·0,25·4)	24·2(21·9,26·9)	23·4(21·2,25·9)
Number missin	0(0)	0(0)	0(0)
Baseline HDL (mg/dL)	47(38,58)	46(37,58)	46(38,58)
Number missing	876(13·0)	274(9·2)	1150(11·9)
Baseline TCHOL (mg/dL)	182(155,211)	187(159,217)	183(155,213)
Number missing	453(6·7)	190(6·4)	643(6·6)
Baseline TRIG (mg/dL)	115(80,167)	126(89,186)	117(82,174)
Number missing	597(8·9)	215(7·2)	812(8·4)
Baseline LDL (mg/dL)	105(85,131)	109(86,133)	106(85,132)
Number missing	4346(64·6)	1664(55·9)	6010(61·9)
Baseline GFR mL/min/1·73 m^2	102(87,113)	98(84,109)	101(86,112)
Number missing	488(7·3)	228(7·7)	716(7·4)
Baseline DBP (mmHg)	75(70,80)	80(75,86)	78(70,82)
Number missing	0(0)	0(0)	0(0)
Baseline SBP (mmHg)	120(110,129)	129(120,136)	121(114,130)
Number missing	0(0)	0(0)	0(0)
ART duration (years)**	9·5(4·6,15·1)	10·6(5·6,16·4)	9·8(4·9,15·6)

Variable†	No incident hypertension (n=6727)	Incident Hypertension (n=2,977)	Total (n=9,704)
Number missing	1511(22·5)	677(22·7)	2188(22·6)
5-year predicted CVD risk (%)	1·8(0·8,3·5)	2·8(1·5,5·2)	2·1(1·0,4·0)
Number missing	911(13·5)	298(10·0)	1209(12·5)
Number of follow-up BP measures	8(4,12)	13(8,18)	9(5,1)
Number missing	0(0)	0(0)	0(0)
Baseline date (mm-yy)	11/15(01/12,04/16)	04/14(01/12,11/15)	09/14(01/12,03/16)
Number missing	0(0)	0(0)	0(0)
Cumulative exposure to NRTIs (years)	9·3(4·6,14·7)	10·3(5·4,15·9)	9·6(4·8,15·1)
Number exposed (%)	5187(77·1)	2292(77·0)	7479(77·1)
Cumulative exposure to NNRTIs (years)	5·8(2·0,10·6)	6·5(2·2,11·3)	6·0(2·1,10·8)
Number exposed (%)	3375(50·2)	1481(49·8)	4856(50·0)
Cumulative exposure to PIs (years)	6·4(2·6,11·6)	6·5(2·7,11·8)	6·5(2·6,11·7)
Number exposed	3665(54·5)	1771(59·5)	5436(56·0)
Cumulative exposure INSTIs (years)	3·0(1·5,4·8)	2·7(0·7,4·8)	3·0(1·4,4·8)
Number exposed	299(4·4)	89(3·0)	388(4·0)
Cumulative exposure to abacavir (years)	4·6(1·7,8·7)	5·3(1·9,9·4)	4·8(1·7,9·0)
Number exposed	1877(27·9)	917(30·8)	2794(28·8)
Cumulative exposure to stavudine (years)	3·2(1·5,5·3)	3·4(1·5,5·5)	3·3(1·5,5·4)
Number exposed	1195(17·8)	669(22·5)	1864(19·2)
Cumulative exposure to nevirapine (years)	1·7(0·3,6·2)	1·8(0·3,5·4)	1·8(0·3,6·0)
Number exposed	850(12·6)	416(14·0)	1266(13·1)
Cumulative exposure to efavirenz (years)	5·8(1·8,10·7)	6·9(2·1,11·3)	6·1(1·9,10·8)
Number exposed	2665(39·6)	1182(39·7)	3847(39·6)
Cumulative exposure to zidovudine (years)	5·4(2·1,8·7)	5·5(2·3,8·6)	5·4(2·1,8·6)
Number exposed	1654(24·6)	765(25·7)	2419(24·9)
Cumulative exposure to darunavir (years)	3·4(1·4,5·7)	3·7(1·3,6·0)	3·4(1·4,5·8)
Number exposed	1395(20·7)	654(22·0)	2049(21·1)
Cumulative exposure to indinavir (years)	1·8(0·7,3·7)	1·9(0·7,3·6)	1·8(0·7,3·6)
Number exposed	731(10·9)	434(14·6)	1165(12·0)
Cumulative exposure to lopinavir (years)	2·8(0·9,6·2)	2·7(1·0,5·8)	2·8(0·9,6·1)
Number exposed (years)	1505(22·4)	691(23·2)	2196(22·6)
Cumulative exposure to TDF[¶] (years)	6·1(3·1,9·3)	6·4(3·3,9·5)	6·2(3·1,9·4)
Number exposed	4168(61·96)	1845(61·98)	6013(61·96)

Table 2:

Baseline characteristics of participants with versus those without incident dyslipidemia

Variable†	No incident dyslipidemia (N=2,542)	Incident dyslipidemia (n=2,689)	Total (n=5,231)
Gender			
Female	807(31·8)	628(23·4)	1435(27·4)
Male	1735(68·3)	2061(76·7)	3796(72·6)
Ethnicity ▫			
White	1718(67·6)	1984(73·8)	3702(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	1253(49·3)	1464(54·4)	2717(51·9)
S. Europe	307(12·1)	285(10·6)	592(11·3)
N. Europe*	982(38·6)	940(35·0)	1922(36·7)
Route of HIV acquisition			
MSM	1121(44·1)	1359(50·5)	2480(47·4)
IDU	328(12·9)	313(11·6)	641(12·3)
Heterosexual	951(37·4)	892(33·2)	1843(35·2)
Other/Unknown	142(5·6)	125(4·7)	267(5·1)
ART Status			
Naive	643(25·3)	686(25·5)	1329(25·4)
Experienced	1899(74·7)	2003(74·5)	3902(74·6)
Prior AIDS			
Yes	449(17·7)	533(19·8)	982(18·8)
No	2093(82·3)	2156(80·2)	4249(81·2)
Hepatitis B infection			
Positive	148(5·8)	140(5·2)	288(5·5)
Negative	2176(85·6)	2269(84·4)	4445(85)
Unknown	218(8·6)	280(10·4)	498(9·5)
Hepatitis C infection			
Positive	1708(67·2)	1798(66·9)	3506(67·0)
Negative	507(19·9)	530(19·7)	1037(19·8)
Unknown	327(12·9)	361(13·4)	688(13·2)
Smoking Status			
Current	753(29·6)	853(31·7)	1606(30·7)
Previous	283(11·1)	312(11·6)	595(11·4)
Never	1013(39·9)	992(36·9)	2005(38·3)
Unknown	493(19·4)	532(19·8)	1025(19·6)
Chronic Kidney Disease			

Variable†	No incident dyslipidemia (N=2,542)	Incident dyslipidemia (n=2,689)	Total (n=5,231)
Yes	139(5·5)	200(7·4)	339(6·5)
No	2398(94·3)	2483(92·3)	4881(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	2375(93·4)	2505(93·2)	4880(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	2260(88·9)	2429(90·3)	4689(89·6)
Unknown	272(10·7)	254(9·5)	526(10·1)
Age (years)	42(34,50)	44(35,51)	43(35,50)
Number missing	0(0)	0(0)	0(0)
Baseline CD4 (cells/μL)	521(360,704)	520(350,711)	520(356,709)
Number missing	0(0)	0(0)	0(0)
Nadir CD4 (cells/μL)	259(145,398)	258(138,391)	258(140,393)
Number missing	0(0)	0(0)	0(0)
Baseline HIV RNA (copies/mL)	39·0(19,499)	39(19,499)	39(19,499)
Number missing	0(0)	0(0)	0(0)
Baseline BMI (kg/m^2)	22·9(20·9,25·3)	23·6(21·4,26·3)	23·3(21·1,25·8)
Number missing	0(0)	0(0)	0(0)
Baseline HDL (mg/dL)	55(46,66)	49(41,58)	52(43,62)
Number missing	277(10·9)	211(7·9)	488(9·3)
Baseline TCHOL (mg/dL)	170(151,191)	182(159,206)	177(155,199)
Number missing	9(0·4)	17(0·6)	26(0·5)
Baseline TRIG (mg/dL)	82(62,109)	106(80,144)	94(71,127)
Number missing	109(4·3)	75(2·8)	184(3·5)
Baseline LDL (mg/dL)	96(80,116)	108(89,128)	101(84,122)
Number missing	1449(57)	1584(58·9)	3033(58·0)
Baseline GFR mL/min/1·73 m^2	103(91,115)	102(87,113)	103(89,114)
Number missing (%)	157(6·18)	211(7·9)	368(7·0)
Baseline DBP (mmHg)	79(70,85)	80(70,85)	80(70,85)
Number missing	131(5·15)	154(5·73)	285(5·5)
Baseline SBP (mmHg)	122(114,134)	125(116,136)	124(115,135)
Number missing	131(5·15)	154(5·73)	285(5·5)
ART duration (years)**	9·7(4·8,15·1)	9·4(4·8,15·0)	9·6(4·8,15·0)
Number missing	643(25·3)	686(25·51)	1329(25·4)
5-year predicted CVD risk (%)	1·4(0·6,2·8)	1·9(0·9,3·5)	1·7(0·8,3·2)
Number missing	374(14·71)	344(12·79)	718(13·7)

Variable†	No incident dyslipidemia (N=2,542)	Incident dyslipidemia (n=2,689)	Total (n=5,231)
Number of follow-up lipid tests	8(4,13)	11(7,17)	10(5,15)
Number missing	0(0)	0(0)	0(0)
Baseline date (mm/yy)	11/14(01/12,06/16)	08/13(01/12,11/15)	05/14(01/12,03/16)
Number missing	0(0)	0(0)	0(0)
Cumulative exposure to NRTIs (years)	9·6(4·7,14·9)	9·2(4·7,14·6)	9·4(4·7,14·8)
Number exposed	1895(74·6)	1997(74·4)	3892(74·4)
Cumulative exposure to NNRTIs (years)	6·5(2·4,11·5)	6·3(2·5,10·9)	6·4(2·4,11·2)
Number exposed	1301(51·2)	1355(50·4)	2656(50·8)
Cumulative exposure to PIs (years)	5·9(2·3,10·7)	6·1(2·5,10·8)	6·0(2·4,10·7)
Number exposed	1256(49·4)	1323(49·2)	2579(49·3)
Cumulative exposure to INSTIs (years)	3·0(1·9,4·4)	3·1(1·7,4·6)	3·1(1·8,4·5)
Number exposed	127(5·0)	126(4·7)	253(4·8)
Cumulative exposure to abacavir (years)	4·4(1·6,9·1)	4·5(1·8,8·8)	4·5(1·7,9·0)
Number exposed	640(25·2)	649(24·1)	1289(24·6)
Cumulative exposure to stavudine (years)	2·7(1·0,5·2)	3·5(1·5,5·6)	3·2(1·2,5·4)
Number exposed	391(15·4)	422(15·7)	813(15·5)
Cumulative exposure to nevirapine (years)	1·1(0·2,4·6)	2·0(0·3,6·0)	1·5(0·2,5·3)
Number exposed	259(10·2)	302(11·2)	561(10·72)
Cumulative exposure to efavirenz (years)	7·1(2·5,11·8)	6·4(2·6,11·1)	6·7(2·6,11·4)
Number exposed	1094(43·0)	1129(42·0)	2223(42·5)
Cumulative exposure to zidovudine (years)	5·3(1·8,8·9)	5·7(2·8,8·6)	5·5(2·3,8·8)
Number exposed	578(22·7)	633(23·5)	1211(23·2)
Cumulative exposure to darunavir (years)	3·2(1·3,5·4)	3·2(1·4,6·1)	3·2(1·3,5·8)
Number exposed	444(17·5)	468(17·4)	912(17·4)
Cumulative exposure to indinavir (years)	2·0(0·8,3·5)	1·9(0·8,4·2)	2·0(0·8,3·9)
Number exposed	259(10·2)	282(10·5)	541(10·3)
Cumulative exposure to lopinavir (years)	2·3(0·7,5·3)	2·1(0·7,4·9)	2·2(0·7,5·1)
Number exposed	467(18·4)	450(16·7)	917(17·5)