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Risk of hypertension in people with HIV in the USA initiating modern antiretroviral regimens: pooled analysis of blood pressure data from five clinical trials

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Background: People with HIV have a greater risk of cardiovascular disease than the general population. Current literature suggests that some ARTs may exacerbate this risk.

Objectives: To estimate the risk of hypertension in treatment-naïve people with HIV receiving integrase strand transfer inhibitor (INSTI)/tenofovir alafenamide (TAF) or INSTI/non-TAF versus NNRTI/non-TAF regimens.

Methods: *Post hoc* pooled analysis evaluating data from US participants in five Phase 3 randomized studies. Adjusted prevalence of Stage 1 and 2 hypertension (American College of Cardiology/American Heart Association criteria) and conditional odds of higher blood pressure ratios were estimated using proportional odds mixed-effect regression through 108 weeks after ART initiation. Time to incident hypertension through 96 weeks was modelled using Cox proportional-hazards regression.

Results: In total, 2411 participants were included (528, 749 and 1134 received NNRTI/non-TAF, INSTI/non-TAF and INSTI/TAF regimens, respectively). Nearly half of participants had hypertension (Stage ≥1) at baseline. The Week 96 adjusted estimates of risk of hypertension (95% CI) were 1.06 (0.99, 1.13) and 1.12 (0.98, 1.27) for Stages ≥1 and ≥2 hypertension, respectively, for NNRTI/non-TAF versus INSTI/non-TAF, and 1.01 (0.95, 1.08) and 1.02 (0.91, 1.17) for Stages ≥1 and ≥2 hypertension, respectively, for NNRTI/non-TAF versus INSTI/TAF. There were no significant differences in conditional odds of high blood pressure between treatment groups. No significant differences were identified in time to incident composite hypertension for INSTI/non-TAF and INSTI/TAF versus NNRTI/non-TAF regimens; estimated hazard ratios (approximate 95% CI) were 0.88 (0.66, 1.17) and 0.98 (0.75, 1.28), respectively.

Conclusions: Results suggest the risk of hypertension is not significantly different across INSTI/TAF, INSTI/non-TAF and NNRTI/non-TAF regimens.

Introduction

Hypertension is a modifiable risk factor for cardiovascular disease (CVD) and major adverse cardiovascular events (MACE), including cardiovascular death, and is common in the general population.[1,2] In 2019, ∼30% of the global population aged 30–79 years were estimated to have hypertension, defined as having systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or taking medication for hypertension.[3]

The risk of CVD in people with HIV is approximately double that of the general population, with CVD and associated events contributing to HIV-related morbidity and mortality.[4,5] Therefore,

HIV is listed as a risk factor for atherosclerotic CVD (ASCVD) by the American College of Cardiology (ACC)/American Heart Association (AHA)[6] and European Society of Cardiology (ESC)[7] guidelines.

People with HIV are more likely to be exposed to traditional risk factors for CVD, such as smoking,[8] alcohol misuse,[9] physical inactivity,[10] low-quality diet,[11] and adverse socioeconomic conditions.[12] However, an increased CVD risk is also apparent in people with HIV without these risk factors and is attributed to a combination of factors, including a chronic inflammatory state resulting from HIV.[4] In addition, current literature suggests that some ARTs may exacerbate CVD risk; however, it is unclear whether risk differs between regimens.[13] Of note, an analysis of 7769 people with HIV conducted as part of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) found a 50% and 42% increased risk of MACE in participants with low-to-moderate risk of CVD with prior or current abacavir use, respectively, compared with those who had never used abacavir. Other ARTs were not associated with an increased risk of MACE in this analysis.[14]

Although it is well recognized that people with HIV are at increased risk of CVD, and that this may be associated with ART, it remains unclear whether particular ART regimens carry increased risk of hypertension. Integrase strand transfer inhibitors (INSTIs) have previously been associated with a higher incidence of hypertension than NNRTIs.[15] Weight gain associated with INSTIs has also been linked to a high risk of blood pressure elevation/hypertension.[16,17] Increasing our understanding of CVD risk and the impact of ART regimens is therefore important to prevent excess cardiovascular events in people with HIV.

In order to evaluate the risk of hypertension in people with HIV, we pooled data from five US multicentre, randomized, double-blind, Phase 3 clinical trials in people with previously untreated HIV. We examined hypertension risk in participants receiving different ART regimens (INSTI versus NNRTI) and types of NRTI [tenofovir alafenamide (TAF) versus non-TAF].

Patients and methods

Ethics

All studies were undertaken in accordance with the Declaration of Helsinki. The study protocols were approved by independent review boards or ethics committees (listed in Table S1, available as Supplementary data at *JAC* Online). No informed consent was obtained to participate in this *post hoc* pooled analysis of existing data; however, all participants provided written informed consent for the primary study analyses.

Original studies

This retrospective *post hoc* pooled analysis evaluated data from US participants in five Phase 3 multicentre, randomized studies [GS-US-264-0110 (NCT01309243),[18] GS-US-292-0104 (NCT01780506),[19] GS-US-292-0111 (NCT01797445),[19] GS-US-380-1489 (NCT02607930),[20–24] and GS-US-380-1490 (NCT02607956)].[21–23,25,26] These five studies were the internal Gilead studies that met the study criteria and had the required data at the time of analysis.

Study 0110 was open-label; all other studies were double-blind, active-controlled trials. All studies enrolled previously ART-untreated adults (aged ≥18 years) with plasma HIV-1 RNA ≥500 copies/mL (Studies 1489 and 1490), ≥1000 copies/mL (Studies 0104 and 0111), or ≥2500 copies/mL (Study 0110) at screening and no known resistance to study drugs.

Participants within each study were randomized 1:1 to receive the following once-daily ART: Study 0110: RPV/FTC/TDF [25/200/300 mg single tablet regimen (STR)] or EFV/FTC/TDF (600/200/300 mg STR); Studies 0104 and 0111: elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF) (150/150/200/10 mg STR) or E/C/F/TDF (150/150/200/300 mg STR); Study 1489: bictegravir/F/TAF (B/F/TAF; 50/200/25 mg STR) or ABC/DTG/3TC (600/50/300 mg STR); and Study 1490: B/F/TAF (50/200/25 mg STR) or DTG (50 mg) with coformulated F/TAF (200/25 mg).

Study 0110 had a follow-up duration of 96 weeks; all other studies had durations of ≥144 weeks. In Studies 1489 and 1490, participants who completed the main study were invited to participate in an open-label extension phase, where participants received B/F/TAF for an additional 96 weeks.

Present analysis: treatment groups and additional inclusion/exclusion criteria

In this *post hoc* pooled analysis, data from US participants were pooled and grouped according to ART drug class (INSTI versus NNRTI) and by regimen within the same NRTI class (TAF versus non-TAF) (Figure S1) as follows: NNRTI/non-TAF: EFV/FTC/TDF or RPV/FTC/TDF (Study 0110); INSTI/non-TAF: E/C/F/TDF or ABC/DTG/3TC (Studies 0104 and 0111, and Study 1489, respectively); INSTI/TAF: E/C/F/TAF, B/F/TAF, or DTG+F/TAF (Studies 0104 and 0111, Studies 1489 and 1490 and Study 1490, respectively). Although these studies also included non-US participants, those individuals were excluded from this analysis to mitigate study-to-study differences in socio-demographic or lifestyle factors that could influence the risk of hypertension (e.g. diet).

We included data for participants who enrolled into any of the five original trials and were from the USA, aged 18–65 years at screening, had systolic and diastolic blood pressure data available at ≥1 study visit and had baseline estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft–Gault formula. Participants in the studies who had used pre-exposure prophylaxis within 45 days before randomization or with prior exposure to an HIV-1 treatment were excluded (in Studies 1489 and 1490, exposure to HIV-1 treatment within 10 days of screening was allowed).

Study outcomes and assessments: statistical analyses

Two analyses were conducted to compare risks of hypertension in participants who received either an INSTI/non-TAF or INSTI/TAF versus an NNRTI/non-TAF regimen: *a primary* analysis to estimate the longitudinal risk of hypertension during follow-up, and a *secondary* analysis to estimate time to incident hypertension up to 96 weeks.

In all studies, blood pressure was measured at baseline and over Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96 and 108 (except for Study 0110, where the last measurement was taken at Week 96) using standard methods uniformly across the studies. Recorded blood pressures were categorized according to the US AHA criteria (heart.org) (Table S2: systolic 130–139 mmHg or diastolic 80–90 mmHg for hypertension Stage 1 and systolic 140–180 mmHg or diastolic ≥90 mmHg for hypertension Stage 2), to aid clinical interpretation. Categorized blood pressures were then modelled directly (primary longitudinal analysis) and used as part of a composite definition for incident hypertension (secondary analysis).

Primary longitudinal analysis

Categorized records of blood pressure were modelled with proportional odds mixed-effect regression using both individual- and study-level random effects. Target estimands included (i) adjusted prevalence of Stage 1

(systolic 130–139 mmHg or diastolic 80–89 mmHg) and Stage 2 (systolic 140–180 mmHg or diastolic ≥90 mmHg) hypertension for each ART regimen (summarizing the population-average treatment effect) and (ii) conditional odds ratios for elevated blood pressure (summarizing the participant-specific treatment effect). These estimands were allowed to depend on the duration of exposure.

Likelihood ratio tests were used to assess null hypotheses about effects of given predictors, including the central null hypothesis that none of the three treatment classes differentially impacts the conditional odds of hypertension.

To mitigate the potential for bias and confounding when pooling data from separate studies, our analyses adjust for key differences in enrolment demographics. Specific baseline factors adjusted for include age, blood pressure, BMI, kidney and liver function (eGFR and ALT, respectively), racial/ethnic identity (Black/White/Other) and sex at birth. Our analysis also adjusted for antihypertensive medication history, including both baseline and in-study initiated use.

We assessed the sensitivity of our primary analysis results to various alternative ways of handling the input data. In particular, we in turn considered (i) excluding records with concurrent antihypertensive medication use; (ii) use of propensity score weighting in addition to covariate adjustment; and (iii) use of an alternative blood pressure category scale.[27] These sensitivity assessments are described further in the Supplementary Materials.

We evaluated the potential effect of uncontrolled confounding by calculating bounds on the inflation of the estimated marginal risk under various scenarios of confounder strength as previously reported.[28] This included an analysis of the potential effects of smoking history, which was not ascertained in all participants and has been shown to be associated with hypertension.[29–31] Details of this analysis are described further in the Supplementary Materials.

Secondary analysis: time to incident hypertension

In the secondary analysis, Cox proportional-hazards regression was used to model time to incident hypertension (composite outcome). An incident hypertension event was defined as the first of: (i) two consecutive records of blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic; (ii) site investigator diagnosis of hypertension as recorded by onset of a hypertension-related adverse event; or (iii) in-trial initiation of antihypertensive medication. Times for individuals who did not experience an incident hypertension event within 96 weeks were right-censored at their last recorded follow-up visit or 96 weeks from their baseline visit (whichever came first). Efron's approximation[32] was used to accommodate ties. For inclusion in the secondary analysis, participants were required to have systolic and diastolic blood pressure data at baseline and no evidence of hypertension within 1 year prior to and including Day 1 (defined as a blood pressure reading of ≥140 mmHg systolic or ≥90 mmHg diastolic, or a medical history of hypertension, or use of antihypertensive medications at screening). Additional details and technical limitations of the secondary analysis are presented in the Supplementary Materials.

Results

Participant baseline demographics and clinical characteristics

In total, 2411 participants were included across the five studies conducted between 2011 and 2021 (Figures S1 and S2). Of these, 528, 749 and 1134 participants received an NNRTI/non-TAF, INSTI/non-TAF, or INSTI/TAF regimen, respectively. The specific ART regimens received are shown in Figure S1. The baseline demographics and clinical characteristics of participants are described in Table 1. The mean ages were 36.3, 35.2 and 34.2 years in the NNRTI/non-TAF, INSTI/non-TAF and INSTI/TAF groups, respectively, and ≥90% of participants in each group were of male sex at birth. Most participants were White (54%–60%). Overall, hypertension (Stage ≥1) was present in nearly half of participants at baseline, yet only 7% were taking antihypertensive medication.

Primary analysis: longitudinal risk of hypertension

After exclusion, over 28 000 total categorized records of blood pressure records were available for analysis through 108 weeks post-ART initiation. In the primary analysis, estimated proportions of participants in each blood pressure category over time aligned closely with the observed data (Figure S3). An assessment of critical modelling assumptions and goodness-of-fit is included in the Supplementary Materials.

Adjusted prevalence of hypertension stage estimated over the pooled sample suggested little to no clinically significant difference in risk across regimens at a group level (Figure 1). At Week 96, the adjusted marginal risk of hypertension for NNRTI/non-TAF versus INSTI/non-TAF was 6% and 12% higher for Stages ≥1 and ≥2 hypertension, respectively, and 1% and 2% higher for Stages ≥1 and ≥2 hypertension, respectively for NNRTI/non-TAF versus INSTI/TAF (Table 2).

Estimated time-varying conditional odds of higher blood pressure for INSTI/TAF or INSTI/non-TAF regimens were not significantly different compared with NNRTI/non-TAF regimens ($P = 0.28$) (Figure 2). Similar findings were seen when the analysis was performed using the European hypertension grading[27] (Figure S4).

Additional baseline factors significantly associated with higher blood pressure during follow-up were age, antihypertensive medication use, BMI, female sex (all $P < 0.001$); Black race ($P = 0.002$); and eGFR ($P = 0.02$).

Sensitivity analyses did not yield meaningfully different results. Withholding records with concurrent antihypertensive medication use (5382 records from 444 participants) did not lead to practical differences in resulting estimation and inference (Figure S5). Similarly, using inverse probability of trial enrolment weighting (trial IPW) in addition to covariate adjustment resulted in better balance across trials and across treatment groups but had little effect on the time-varying odds ratios for the INSTI/non-TAF versus NNRTI/non-TAF and INSTI/TAF versus NNRTI/non-TAF comparisons (Figure S6).

Evaluation of the potential impact of uncontrolled confounder–hypertension effects (specifically smoking status) are shown in Table S3. The results suggest that it is implausible that smoking could confound the relationship between treatment and hypertension to a degree that would change the conclusions we draw from our primary analysis.

Secondary analysis: time to incident composite hypertension event

Of the 2238 participants with no evidence of hypertension at baseline, 425 (19%) experienced hypertension events over the duration of the analysis. Of these, 171 (8%) had consecutive blood pressure records indicating Stage ≥2 hypertension; 169 (8%) initiated antihypertensive medications; and 85 (4%) experienced hypertension-related adverse events as their first recorded

Table 1. Baseline demographics and clinical characteristics

	NNRTI/non-TAF ($n=528$)	INSTI/non-TAF ($n=749$)	INSTI/TAF ($n=1134$)	χ^{2a}
Age,[b] years, mean (SD)	36.3 (10.7)	35.2 (10.8)	34.2 (11.1)	26.9
Male sex at birth,[b] *n* (%)	493 (93)	671 (90)	1024 (90)	19.0
Race,[b] *n* (%)				
Black	171 (32)	294 (39)	466 (41)	38.1
White	318 (60)	404 (54)	612 (54)	
Other	38 (7)	51 (7)	56 (5)	
BMI,[b,c] kg/m^2, mean (SD)	26.3 (4.9)	26.4 (5.6)	26.5 (5.8)	2.8
eGFR,[b] mL/min/1.73 m^2, mean (SD)	117.9 (29.5)	124.8 (34.2)	128.8 (37.7)	71.3
Alanine aminotransferase, units/L	33.3 (26.1)	30.7 (25.4)	30.1 (24.6)	—
Systolic blood pressure,[b] mmHg, mean (SD)	120.8 (13.5)	122.8 (13.8)	122.6 (13.0)	9.2
Diastolic blood pressure,[b] mmHg, mean (SD)	77.2 (9.7)	77.1 (9.7)	77.4 (9.7)	5.3
Hypertension (Stage 1), *n* (%)	182 (35)	255 (34)	390 (34)	8.8
Hypertension (Stage 2), *n* (%)	70 (13)	114 (15)	165 (15)	
Use of antihypertensives,[d] *n* (%)	39 (7)	52 (7)	76 (7)	8.6
CD4 count,[e] cells/μL, mean (SD)	—	449.9 (242.9)	433.8 (237.1)	—
HIV-1 RNA,[f] $\log_{10}$ copies/mL, mean (SD)	—	4.5 (0.7)	4.5 (0.7)	—

The key covariates included in the models are shown; additional variables were either not available for all participants or did not contribute to model performance.

CD, cluster of differentiation; eGFR, estimated glomerular filtration rate; INSTI, integrase strand transfer inhibitor; SD, standard deviation.

[a]Measure of cross-study discrepancy (higher values = more discrepancy): degree of freedom parameter = 4 (8 for race).

[b]Model covariate.

[c]Data not available for one participant.

[d]Participants using antihypertensives at or before baseline.

[e]Data not available for 529 participants.

[f]Data not available for 528 participants.

hypertension event (Figure 3). The proportion of participants initiating antihypertensives post-baseline was similar between regimens over the duration of the study, with 54 (10%), 80 (11%) and 143 (13%) of participants in the NNRTI/non-TAF, INSTI/non-TAF and INSTI/TAF groups initiating antihypertensives post-baseline (Table 3).

Consistent with the primary analysis, INSTI/non-TAF and INSTI/TAF regimens were associated with a similar or slightly increased (lower HR) time to incident composite hypertension event compared with NNRTI/non-TAF regimens. HRs (approximate 95% CI) were 0.88 (0.66, 1.17) and 0.98 (0.75, 1.28) for INSTI/non-TAF and INSTI/TAF regimens, respectively (Figure 3).

Discussion

This *post hoc* analysis of five large, randomized clinical trials pooled data from 2411 people with HIV and over 28 000 longitudinal blood pressure assessments collected over 108 weeks. We found that risk of hypertension (Stages ≥1 or ≥2) was similar across different ART regimens (NNRTI/non-TAF, INSTI/TAF and INSTI/non-TAF). There were no significant differences in the estimated time-varying conditional odds of higher blood pressure between the groups, and the findings were similar with European hypertension grading, suggesting the results are not sensitive to the different hypertension scales. However, the higher systolic and diastolic blood pressure cutoffs applied by the European hypertension categories resulted in lower observed rates of hypertension overall. The impact of different ART regimens on hypertension risk was reviewed recently and no consistent trends were reported; some studies suggested elevated risks of hypertension with dolutegravir while other studies showed no differences in risk compared with other ARTs.[13] Our data showed no significant differences across ART regimens and add to the growing evidence base regarding the impact of ARTs on CVD risk factors. Several mechanisms are thought to contribute to an increased risk of hypertension in people with HIV and undergoing ART, including microbial gut translocation, chronic inflammation, immune reconstitution, lipodystrophy, dyslipidemia, adipocytokines, neuroendocrine responses, HIV-related renal disease and ART-related effects.[4,33] Regardless of ART regimen, we found a high incidence of hypertension in this sample of relatively young people with HIV taking first-line ART. At baseline ∼50% of participants (with a mean age of only 34.2–36.3 years) had Stage ≥1 hypertension. By comparison, an analysis of hypertension in the general population of US adults reported an age-adjusted prevalence of 31% for men aged 18–39 years.[34] Although our study population included a broader age group (18–65 years), our findings nonetheless suggest that hypertension was more prevalent in our cohort of participants with HIV than could be expected in a similar cohort of individuals without HIV.[35]

Although approximately half of participants had Stage ≥1 hypertension, only 7% were taking antihypertensive medication at baseline. In addition to this high level of Stage 1 hypertension at baseline, following ART initiation, blood pressure–related events (initiation of antihypertensives, adverse events and Stage ≥2 hypertension) occurred in 19% of participants over a

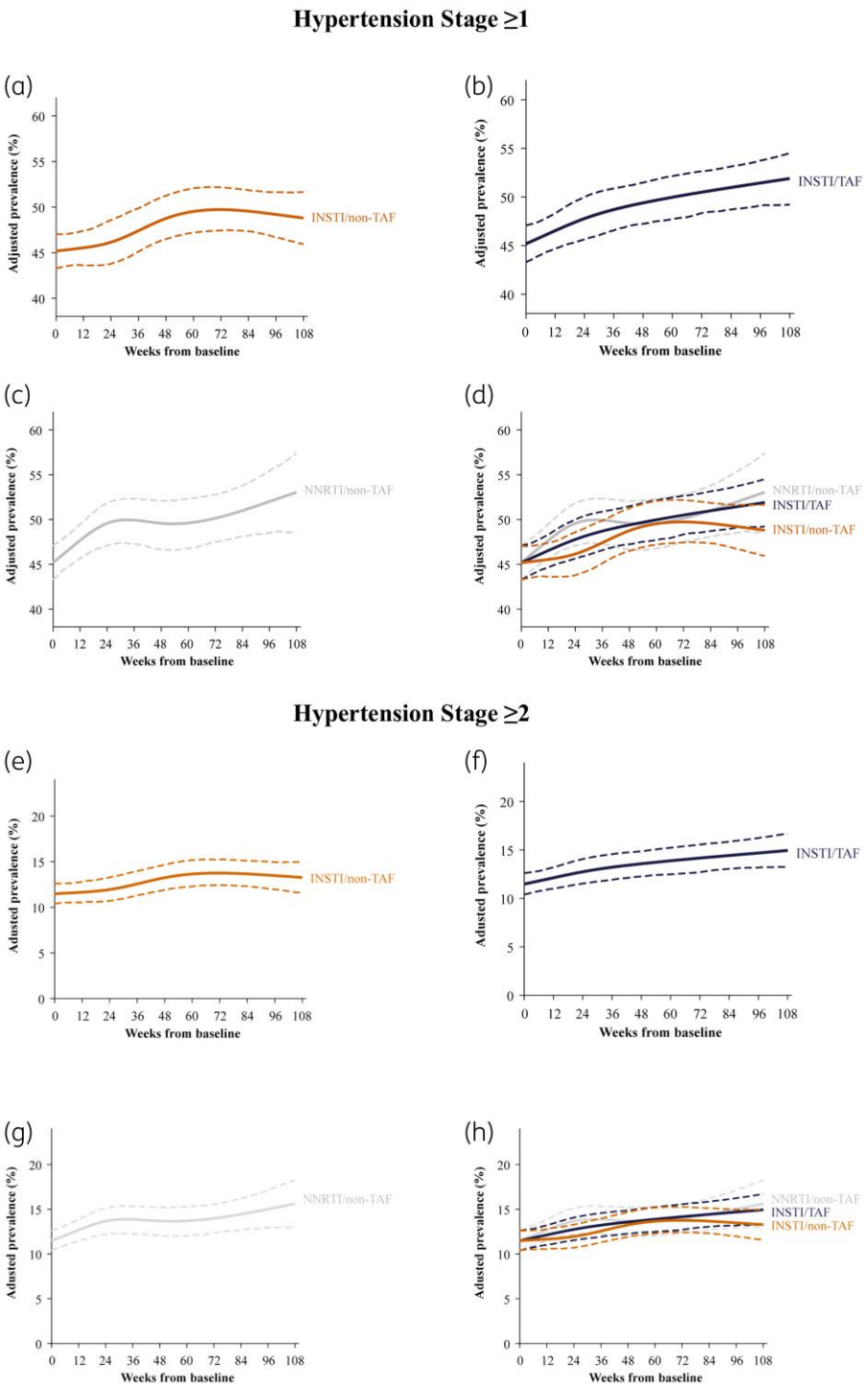


Figure 1. Primary analysis: adjusted prevalence of hypertension stages (inter-participant). The adjusted prevalence of Stage ≥1 hypertension (a–d) and Stage ≥2 hypertension (e–h) is shown individually for each treatment group (a–c and e–g) and combined (d and h). Solid lines show estimated rates as a function of time and treatment for participants who never take antihypertensives; dashed lines show pointwise 95% CIs. Note the different *y*-axis ranges in the Stage ≥1 hypertension figures (40%–60%) versus the Stage ≥2 hypertension figures (0%–20%) due to the higher prevalence of Stage ≥1 than Stage ≥2 hypertension. Prevalence estimates are adjusted for baseline covariates, including age, ALT, BMI, eGFR, sex assigned at birth, race, systolic and diastolic blood pressure and use of antihypertensives. Stage 1 hypertension was defined by the American Heart Association as 130–139 mmHg systolic blood pressure or 80–89 mmHg diastolic blood pressure. Stage 2 hypertension was defined by the American Heart Association as 140–180 mmHg systolic blood pressure or ≥90 mmHg diastolic blood pressure. INSTI, integrase strand transfer inhibitor.

Table 2. Adjusted estimates of risk of hypertension ratios at Week 96 (95% CI)

	Hypertension grade	
Comparison	Stage ≥1	Stage ≥2
NNRTI/non-TAF versus INSTI/non-TAF	1.06 (0.99, 1.13)	1.12 (0.98, 1.27)
NNRTI/non-TAF versus INSTI/TAF	1.01 (0.95, 1.08)	1.02 (0.91, 1.17)

Estimates were derived from the primary analysis and are adjusted for baseline covariates, including age, ALT, BMI, eGFR, sex assigned at birth, race, systolic and diastolic blood pressure and use of antihypertensives. Stage 1 hypertension was defined by the American Heart Association as 130–139 mmHg systolic blood pressure or 80–89 mmHg diastolic blood pressure.
INSTI, integrase strand transfer inhibitor.

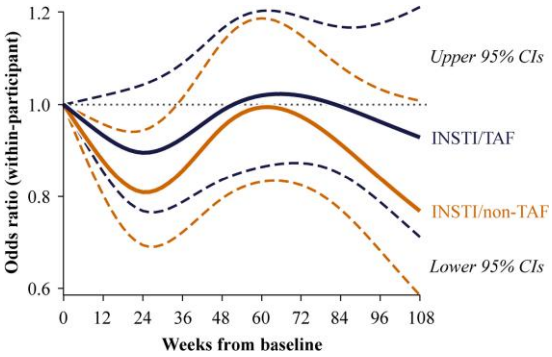


Figure 2. Primary analysis: conditional odds of higher blood pressure (intra-participant); comparator: NNRTI/non-TAF. Solid lines show estimates of conditional (within-participant) odds ratios of higher blood pressure categories (i.e. Stage 1 or 2 hypertension versus elevated or normal blood pressure) as a function of time on treatment for INSTI/TAF and INSTI/non-TAF treatments versus NNRTI/non-TAF treatment; dashed lines show pointwise 95% CIs. The horizontal dotted line denotes even odds with NNRTI/non-TAF treatments. INSTI, integrase strand transfer inhibitor.

relatively short period of time. These findings suggest that, for some participants, progression to clinical hypertension may have been a relatively recent development, could have been related to anxiety on being screened to start ART, or might be 'white coat hypertension'. Additionally, 'return to health' may contribute to new incidences of hypertension and other comorbidities experienced by the general population, for example, age-related increases in myocardial infarction, end-stage renal disease, cancer and diabetes.[36,37]

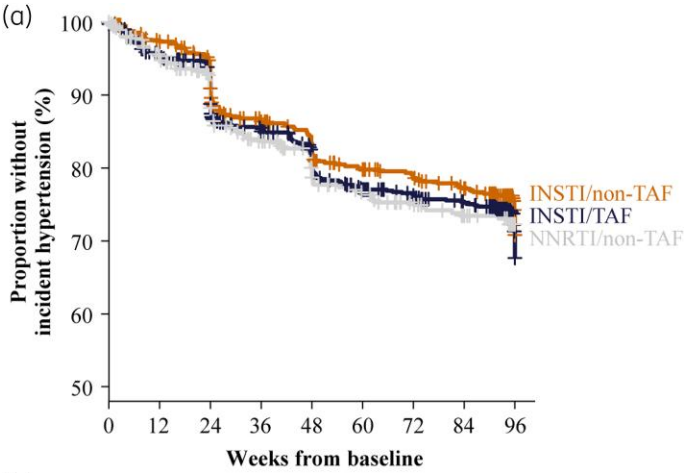
With the introduction of more effective ARTs and the emergence of CVD as a major cause of morbidity and mortality in an ageing population of people with HIV,[38] timely diagnosis and treatment of hypertension is crucial to prevent adverse outcomes, including ASCVD and kidney failure, which have been associated with hypertension and are more prevalent in people with HIV compared with the general population.[39,40] Non-pharmacological interventions are recommended by CVD guidelines for all adults with elevated blood pressure or hypertension, with pharmacological interventions recommended for those with an elevated 10-year CVD risk of 10% or higher.[41] In addition, the REPRIEVE study demonstrated the benefit of initiating statins in people with HIV, even for those with a low-to-moderate risk of CVD.[42] Given the well-established benefits of blood pressure control on clinical outcomes, our findings highlight the need for careful monitoring of blood pressure, even in young people with HIV.

Unlike many previous analyses,[33] our current study focused on previously ART-untreated participants. Non-suppressed HIV has been associated with an increased incidence of CVD,[43] and of hypertension, which may be due to factors including immune activation, endothelial dysfunction, microbial translocation and renal disease.[33] Increased immune activation associated with HIV infection has been shown to cause arterial inflammation, which can continue even following effective ART, and is considered to be an important factor in the pathophysiology of ASCVD in people with HIV.[4] Furthermore, HIV proteins such as Nef have been implicated in defective cholesterol transport and accumulation in macrophages, which may also contribute to CVD risk in this population.[44]

The use of INSTIs in ART regimens has previously been associated with an increased incidence of arterial hypertension,[15] although a large cohort study found no significantly increased risk of CVD with this drug class (adjusted HR for INSTI-based ART versus other ART: 0.80; 95% CI: 0.46, 1.39) and the adjusted risk difference for INSTI-based ART versus other ART after 8 years was −0.71% (95% CI: −2.16, 0.94).[45]

Hypertension represents a major modifiable cardiovascular risk factor in people with HIV, with incident hypertension potentially contributing to the elevated CVD burden observed in this population.[5,13,38] Understanding factors that influence blood pressure in individuals with HIV is therefore clinically important for CVD prevention strategies. Weight gain may serve as a key mediating pathway through which antiretroviral medications influence hypertension risk, particularly with INSTIs (with and without TAF).[46–48] Some studies have suggested that TAF regimens in particular may be associated with increases in blood pressure, perhaps associated with increases in weight when switching from TDF to TAF.[4,49] However, recent data suggest that this effect may in part be attributed to viral suppression leading to a 'return to health' phenomenon, a return to normal age-associated societal weight gain and removal of the weight-suppressive effect of TDF in people switching from TDF to TAF.[50] The 'return to health' effect is supported by results from studies showing greater weight gain with ARTs for people with advanced HIV disease at baseline (as assessed by CD4 counts, HIV-1 RNA and symptomatic HIV).[48,51] Weight gain has also been observed in people with certain *CYP2B6* polymorphisms when switching from EFV to DTG, possibly due to removal of the weight-suppressive effect of higher EFV concentrations in these individuals.[52] The findings from our analysis suggest that TAF, at least in combination with INSTIs, does not result in an increased risk of hypertension relative to other commonly prescribed treatments. In our analysis, we adjusted for BMI at baseline. Future studies may consider the extent to which weight gain during the course of treatment mediates hypertension risk and to what extent this

(a)



(b)

Composite hypertension events measured during follow-up at Week 24, 48, or 96	
Total events, n (%)	**425 (19)**
Consecutive blood pressure records indicating Stage ≥2 hypertension	171 (8)
Initiation of antihypertensive medication	169 (8)
Hypertension-related adverse event	85 (4)

Figure 3. Secondary analysis: Time to incident composite hypertension event. The Kaplan–Meier plot (a) shows proportion without incident hypertension over time for each treatment group. Data points show censoring times. Curves are not adjusted for demographic differences in the study samples. The composite hypertension events table (b) shows the component events that came first, not the total number. Hypertension-related adverse events included accelerated and essential hypertension. INSTI, integrase strand transfer inhibitor.

risk is offset by lifestyle interventions designed to promote weight loss.

This pooled analysis does have some limitations. Firstly, the use of blood pressure categories, rather than continuous blood pressure values, may render the analysis less sensitive to small changes. In addition, variability in practices for blood pressure measurement across studies and study sites—including differences in devices, caffeine intake and rest before taking measurements—may have led to under- or over-estimation of blood pressure.[53] However, given the size of the cohort, this is unlikely to have been severe or frequent enough to significantly impact our results.

Secondly, some of the data included in this pooled analysis extend back to studies initiated in 2011, and the prevalence of hypertension, as well as treatments, have evolved in the interim (although methods of blood pressure monitoring have largely remained unchanged). In addition, as no participants were taking an NNRTI/TAF regimen, the effect of this ART regimen could not be included, and conclusions cannot be drawn on the blood pressure effects of TAF in the absence of an INSTI.[4,49,50]

Finally, data from these US cohorts of controlled clinical trials may differ from people seen in routine HIV clinical practice. For example, participants were relatively young, mostly of non-Hispanic White ethnicity, and with mostly well-controlled HIV, which may limit the generalizability of these findings to broader HIV populations. We adjusted for major clinical predictors of hypertension to reduce effects of potential confounding over our pooled sample and to promote generalizability of our results to broader HIV populations. However, for some participants, potentially important data—such as viral load, diet and smoking history—were not available. Our assessment of covariate confounders suggests that unadjusted confounding would not have had a substantial impact on the primary analysis results in this population. Note that generalizability may extend to relative measures of treatment effect like the odds ratios we report in Figure 2, or the hazard ratios in the results section, but not directly to the prevalence results in Figure 1.

Table 3. Use of antihypertensive medication

	Participants using antihypertensives at baseline	Participants initiating antihypertensives post-baseline
NNRTI/non-TAF, $n=528$	39 (7)	54 (10)
INSTI/non-TAF, $n=749$	52 (7)	80 (11)
INSTI/TAF, $n=1134$	76 (7)	143 (13)

All values shown as *n* (%).
INSTI, integrase strand transfer inhibitor.

Conclusions

Results of this *post hoc* analysis suggest risk of hypertension is not significantly different across INSTI/TAF, INSTI/non-TAF and NNRTI/non-TAF treatments. Baseline hypertension (Stage ≥1) was present in ∼50% of this pooled sample of relatively young people with HIV taking first-line ART, yet few were taking antihypertensive medication. In addition, blood pressure–related events (initiation of antihypertensives, adverse events, or Stage ≥2 hypertension) occurred in 19% of participants over 2 years of follow-up. Recognizing that hypertension is multifactorial in nature, our study highlights the need for careful monitoring and appropriate treatment of hypertension in similar populations, regardless of ART choice.

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Supplementary data

Figures S1 to S6 and Tables S1 to S3 are available as Supplementary data at *JAC* Online.

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