Risk of Hypertension in Treatment-Naïve People With HIV in the US Receiving INSTI Versus NNRTI, or TAF– Versus Non-TAF–Based Regimens: Pooled Analysis of Blood Pressure Data From Five Clinical Trials

P283

NCT01309243, NCT01780506, NCT01797445, NCT02607930, NCT02607956

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Conclusions

- Baseline hypertension (Grade: Stage ≥ 1) was present in ~50% of this sample of relatively young people with HIV taking first-line ART, yet few were taking antihypertensive medication
- INSTI/TAF and INSTI/non-TAF treatments showed similar or slightly lower odds of hypertension than NNRTI/non-TAF treatment
- Blood pressure–related events (initiation of antihypertensives, adverse events, and Stage ≥ 2 hypertension) occurred in 19% of participants over a relatively short time
- This analysis highlights the need for careful monitoring and appropriate treatment of hypertension in this population, regardless of ART choice

Plain Language Summary

- High blood pressure is associated with a bigger risk of stroke and heart attack
- People with human immunodeficiency virus (HIV) have a high risk of developing heart problems, possibly because of more swelling (inflammation) in their bodies
- Some HIV medicines have also been reported to raise this risk, but there is no agreement on this or if the risk is different based on treatment
- In this study, we looked to see if different HIV medicines have any effect on blood pressure in people with HIV
  - We used combined data from five studies that included more than 2400 people
- After 2 years, there was no clear difference in the risk of high blood pressure in people receiving different HIV treatments

Introduction

- Hypertension, a modifiable risk factor, is relatively common in the general population and contributes to the increasing burden of cardiovascular disease (CVD) globally[1,2]
- People with HIV (PWH) are at increased risk of CVD and associated events, which contributes to HIV-related morbidity and mortality[3]
  - Recent studies have suggested that certain antiretroviral therapies (ARTs) may exacerbate cardiovascular risk (for instance, more hypertension on an integrase strand transfer inhibitor [INSTI] vs non-INSTI or tenofovir alafenamide [TAF] vs non-TAF); however, it is unclear how risk differs between ART regimens and drug classes[4]
- In PWH receiving ART, with low-to-moderate risk of CVD, early initiation of statins has been shown to substantially reduce the risk of major adverse cardiovascular events (hazard ratio: 0.65; 95% CI: 0.48, 0.90; *P* = 0.002)[5]
- Understanding the risk of CVD in PWH is therefore crucial to enable early interventions to improve outcomes

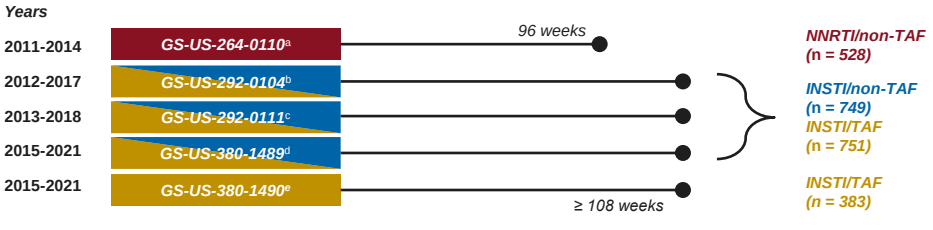
Objectives

- Primary: To assess differences in the risk of hypertension during follow-up in clinical trials between participants who received either an INSTI/non-TAF or INSTI/TAF versus a non-nucleoside reverse transcriptase inhibitor (NNRTI)/non-TAF regimen
- Secondary: To estimate differences in the time to incident hypertension (composite outcome) up to 96 weeks of follow-up across the same treatment groups with no evidence of hypertension at baseline

Methods

Study Design

- In this *post hoc* analysis, US participants' data were pooled from five randomized, double-blind, Phase 3 studies including adults with HIV receiving NNRTI/non-TAF, INSTI/non-TAF, or INSTI/TAF regimens as first-line ART[6-10]



[a]NCT01309243, treatment groups: RPV/F/TDF STR vs EFV/F/TDF.[6] [b]NCT01780506, treatment groups: EVG/COBI/F/TAF (STR) vs EVG/COBI/F/TDF (STR).[7] [c]NCT01797445, treatment groups: EVG/COBI/F/TAF (STR) vs EVG/COBI/F/TDF (STR).[8] [d]NCT02607930, treatment groups: B/F/TAF (STR) vs ABC/DTG/3TC (STR).[9] [e]NCT02607956, treatment groups: B/F/TAF (STR) vs DTG + F/TAF multi-tablet regimen.[10]
3TC, lamivudine; ABC, abacavir; B, bictegravir; COBI, cobicistat; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; F, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RPV, rilpivirine; STR, single tablet regimen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Participant data were grouped by ART drug class (INSTI vs NNRTI) and by regimen within the same nucleoside/nucleotide reverse transcriptase inhibitor class (TAF vs non-TAF)

HIV-1 ART Classes and Regimens

ART Class	ART Regimen
NNRTI/non-TAF	**EFV/FTC/TDF** (272; 52%), **RPV/FTC/TDF** (256; 48%)
INSTI/non-TAF	**E/C/F/TDF** (518; 69%), **ABC/DTG/3TC** (231; 31%)
INSTI/TAF	**E/C/F/TAF** (524; 46%), **B/F/TAF** (418; 37%), **DTG + F/TAF** (192; 17%)

3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; B, bictegravir; C, cobicistat; DTG, dolutegravir; E, elvitegravir; EFV, efavirenz; F/FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Statistics

- In the primary analysis, over 30,000 longitudinal blood pressure records were graded by hypertension severity according to the American College of Cardiology/American Heart Association criteria[11] and modeled with proportional odds mixed-effect regression through 108 weeks post-treatment initiation[a]
- In the secondary analysis, time to incident composite hypertension event by treatment and blood pressure category through 96 weeks post-initiation was modeled using Cox proportional hazards regression[a]

[a]Inverse propensity of trial enrollment weighting was also applied, yielding results consistent with the uniformly weighted analysis.

Outcome Definitions

- Primary analysis: Blood Pressure Grading Scale[11]

Grade[a]	Systolic Blood Pressure, mm Hg		Diastolic Blood Pressure, mm Hg
Normal	< 120	and	< 80
Elevated	120-129	and	< 80
Hypertension (Stage 1)	130-139	or	80-90
Hypertension (Stage 2)	≥ 140-180	or	≥ 90

[a]Using the grading scale from the American Heart Association (heart.org); individuals with systolic and diastolic blood pressure in two categories should be designated to the higher blood pressure category.

- Secondary analysis: Composite hypertension event was defined as the first occurrence of a hypertension-related adverse event, initiation of antihypertensive medication, or consecutive blood pressure records indicating Stage ≥ 2 hypertension

Results

Baseline Demographics and Clinical Characteristics

	NNRTI/Non-TAF (n = 528)	INSTI/Non-TAF (n = 749)	INSTI/TAF (n = 1134)	$\chi^{2,a}$
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 (%)				
White	318 (60)	404 (54)	612 (54)	38.1
Black	171 (32)	294 (39)	466 (41)	
Other	38 (7)	51 (7)	56 (5)	
BMI,[b,c] kg/m², mean (SD)	26.3 (4.9)	26.4 (5.6)	26.5 (5.8)	2.8
eGFR,[b] mL/min/1.73 m², mean (SD)	117.9 (29.5)	124.8 (34.2)	128.8 (37.7)	71.3
Systolic blood pressure,[b] mm Hg, mean (SD)	120.8 (13.5)	122.8 (13.8)	122.6 (13.0)	9.2
Diastolic blood pressure,[b] mm Hg, 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)	–

[a]Measure of cross-study discrepancy (higher values = more discrepancy): degree of freedom parameter = 4. [b]Model covariate. [c]Data missing for one participant. [d]Participants using antihypertensives at or before baseline. [e]Data missing for 529 participants. [f]Data not available for 528 participants.
BMI, body mass index; CD4, cluster of differentiation 4; eGFR, estimated glomerular filtration rate; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; TAF, tenofovir alafenamide.

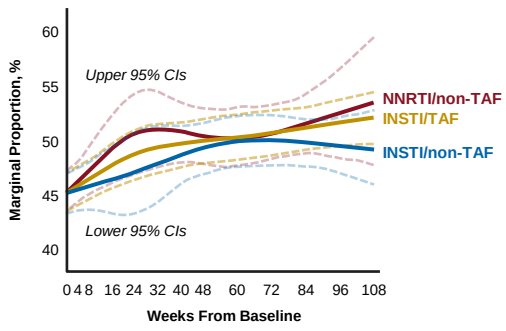
- Overall, baseline characteristics and covariates are well balanced across the five studies

Primary Analysis: Marginal Proportions of Hypertension Stages (Inter-Participant)

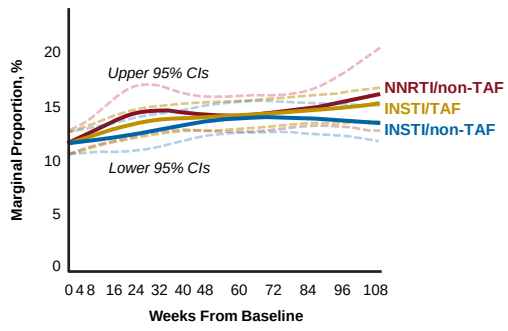
- Adjusted prevalence of hypertension stage estimated over the pooled sample suggests no statistically significant differences in risk across treatments

Scan the QR code for blood pressure categories by treatment and sensitivity analyses using EU hypertension categories

Hypertension Stage ≥ 1



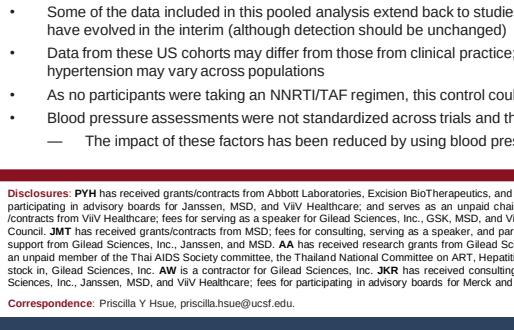
Hypertension Stage ≥ 2



The dashed gray line is the null value, indicating even odds with the reference group (NNRTI/non-TAF); 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 distinct marginal proportion ranges in the Stage ≥ 1 hypertension figure on the left (40-60%) versus the Stage ≥ 2 hypertension figure on the right (0-20%).
Marginal proportions/HRs were adjusted for baseline covariates, including age, alanine aminotransferase, BMI, eGFR, sex assigned at birth, race, systolic and diastolic blood pressure, and use of antihypertensives. All study participants were included regardless of baseline blood pressure category. Stage 1 hypertension defined by the American Heart Association as 130-139 mm Hg systolic blood pressure or 80-89 mm Hg diastolic blood pressure.
BMI, body mass index; eGFR, estimated glomerular rate; HR, hazard ratio; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; TAF, tenofovir alafenamide.

Primary Analysis: Conditional Odds of Higher Blood Pressure (Intra-Participant)

Risk of Higher Hypertension Stage (Comparator: NNRTI/Non-TAF)

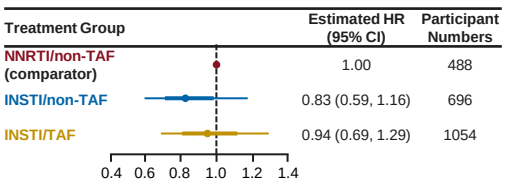


- Intra-participant risk of hypertension was modeled
- Compared with NNRTI/non-TAF treatment, INSTI treatments were associated with similar or slightly lower odds of higher hypertension stage (*P* = 0.24)

Solid lines show estimates of conditional (within-participant) odds ratios of higher blood pressure categories (eg, Stage 1 or 2 hypertension vs elevated or normal blood pressure) for INSTI/TAF and INSTI/non-TAF treatments versus NNRTI/non-TAF treatment (dashed lines: pointwise 95% CIs).
Interaction with treatment estimate shown is for a 35-year-old person with HIV and normal eGFR (≥ 60 mL/min/1.73 m²).
eGFR, estimated glomerular filtration rate; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; TAF, tenofovir alafenamide.

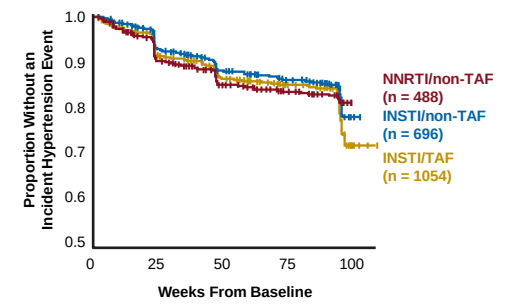
Secondary Analysis: Time to Incident Composite Hypertension Event

Incident Hypertension Events in Participants With No Evidence of Hypertension at Baseline (N = 2238)



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)

Hypertension-Free Participants, by Treatment



Scan the QR code for antihypertensive medication initiations by group

Marginal proportions/HRs in the Forest plot above were adjusted for baseline covariates, including age, alanine aminotransferase, BMI, eGFR, sex at birth, race, and systolic and diastolic blood pressure.
Thin lines indicate approximate 95% CIs, thick lines indicate SEs. Participants with hypertension at baseline (existing diagnoses and/or receiving antihypertensive medication) were excluded (n = 173).
BMI, body mass index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; TAF, tenofovir alafenamide.

The primary analysis showed similar or slightly lower odds of higher hypertension stage in the INSTI groups versus the NNRTI/non-TAF group; the secondary analyses support these findings

Limitations

- 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 detection should be unchanged)
- Data from these US cohorts may differ from those from clinical practice; although treatment effects may still be similar, the impact of risk factors for hypertension may vary across populations
- As no participants were taking an NNRTI/TAF regimen, this control could not be included
- Blood pressure assessments were not standardized across trials and there may have been regional differences in testing
  - The impact of these factors has been reduced by using blood pressure categories, although this approach may miss within-category changes

References: **1.** Mills KT, et al. *Nat Rev Nephrol.* 2020;16:223-37. **2.** Vaduganathan M, et al. *J Am Coll Cardiol.* 2022;80:2361-71. **3.** Obare LM, et al. *Circ Res.* 2024;134:1515-45. **4.** Hill A, et al. *Curr Opin HIV AIDS.* 2024;19:21-9. **5.** Grinspoon SK, et al. *N Engl J Med.* 2023;389:687-99. **6.** NCT01309243. https://clinicaltrials.gov/study/NCT01309243 (accessed Aug. 15, 2024). **7.** NCT01780506. https://clinicaltrials.gov/study/NCT01780506 (accessed Aug. 15, 2024). **8.** NCT01797445. https://clinicaltrials.gov/study/NCT01797445 (accessed Aug. 15, 2024). **9.** NCT02607930. https://clinicaltrials.gov/study/NCT02607930 (accessed Aug. 15, 2024). **10.** NCT02607956. https://clinicaltrials.gov/study/NCT02607956 (accessed Aug. 15, 2024). **11.** Whelton PK, et al. *Hypertension.* 2018;71:1269-324.

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