



# Risk factors for incident hypertension within one year of initiating antiretroviral therapy (ART) among people with HIV.

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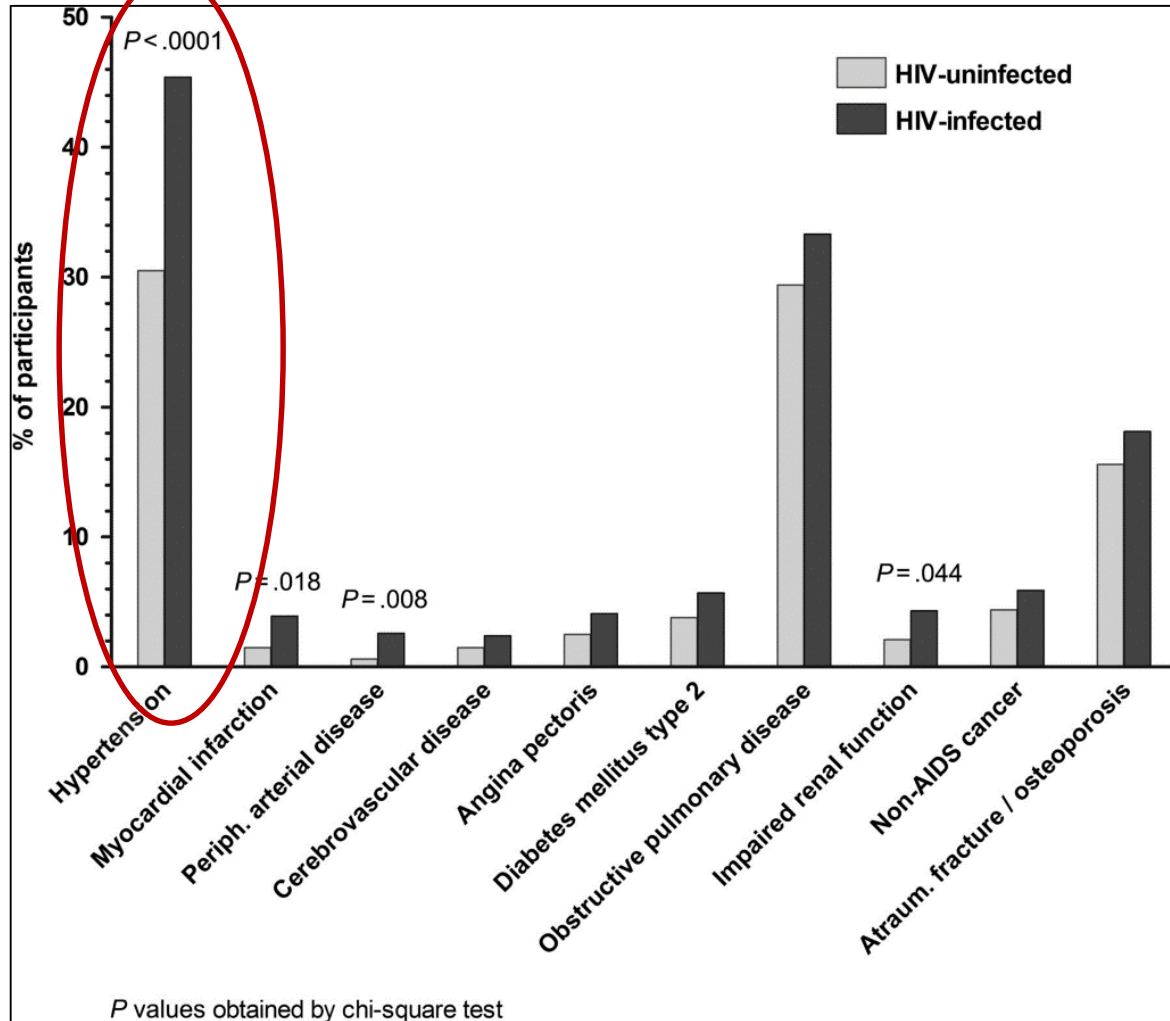
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# Cross-sectional Comparison of Comorbidity Prevalence

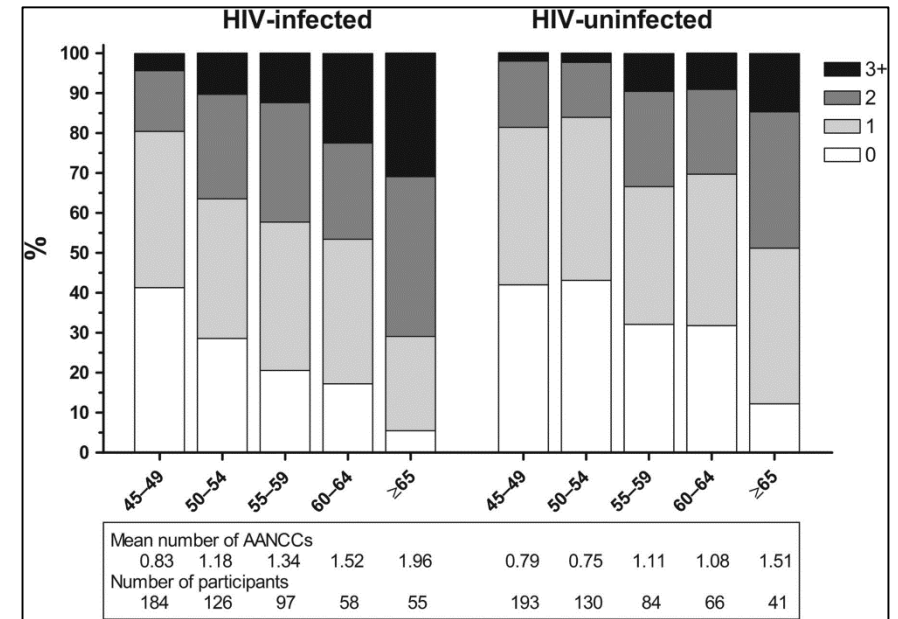
## The AGE<sub>n</sub>IV Cohort Study

### Comorbidity Prevalence by HIV Status



### Comorbidities with ↑ Prevalence

- HTN
- CVD
- Peripheral Artery Disease
- CKD



***HIV appears to accelerate the prevalence of Multimorbidity.***

# Background

- Hypertension is long recognized as a key modifiable risk factor for cardiovascular disease.
  - Increased risk for myocardial infarction (MI), stroke, coronary artery disease (CAD), chronic kidney disease (CKD), and peripheral vascular disease (PAD).
- Prevalence of HTN in the United States is estimated to be 29% (NHANES 2015-16)
- Hypertension is a common co-morbidity among people living with HIV (PLWH) and its prevalence is higher among PLWH than in those without
  - Estimated 42% have HTN from the Medical Monitoring Project.
- HTN among PLWH has been linked with traditional risk factors
  - age, obesity, history of ASCVD or CKD, and family history of HTN
- Limited and conflicting data about the relationship of ART initiation and development of HTN.

## Methods

- AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT): longitudinal cohort study of PLWH randomized prospectively into clinical trials
- We included participants from seven ART-naïve studies
  - ACTG 347, 384, 388, A5014, A5095, A5142, and A5202
- Prospective follow-up begins when a participant entered their parent trial
- Standardized assessments are conducted every 12 weeks during the parent protocol and every 16 weeks after completion of the protocol and enrollment in ALLRT

# Methods

- Physical measures included height, weight, waist circumference, hip circumference, and systolic and diastolic blood pressure.
  - Standardized BP collection used in ALLRT
    - 5 minutes sitting alone
- Laboratory assays included glucose, lipid profile, hematology, serum creatinine, CD4 counts, and HIV viral loads.
- Standardized assessments are conducted every 12 weeks during the parent protocol and every 16 weeks after completion of the protocol and enrollment in ALLRT.
- Smoking status (current or former, never) and intravenous drug use (current or former, never) were defined via self-report at baseline.

# Methods

- We calculated descriptive statistics (mean, standard deviation, median, interquartile range (IQR), frequency and percentages) for the study population overall at baseline.
- Outcome variable: Incident Hypertension defined as
  - Systolic blood pressure (SBP)  $\geq 140$  mm Hg
  - Diastolic blood pressure (DBP)  $\geq 90$  mm Hg
  - Initiation of antihypertensive medication or
  - Clinical diagnosis of hypertension
- We assessed demographic, clinical, and lifestyle factors associated with incident hypertension at 48 weeks.
- Poisson regression with robust variance estimators was used to assess the association of ART agents and classes with incident hypertension at 48 weeks for people free of hypertension at baseline.
  - Unadjusted regression analyses and further performed a multivariable analysis including covariates selected *a priori* (age, body mass index, gender, race/ethnicity, current smoking, low eGFR, and diabetes).
  - We further allowed for variables to remain in the adjusted model if they were significantly associated with incident hypertension in univariate analysis ( $p < 0.1$ ).
- Risk ratios and 95% confidence intervals were calculated.
  - All analyses assumed two-sided  $p$ -values as statistically significant if  $p \leq 0.05$ .

## Results: Participant Inclusion in Analysis

Criteria	No. included	No. excluded
Initial study population	7073	0
Participants in the United States	6913	160
Participants identifying as white, Black, or Hispanic	6714	199
Participants with a baseline blood pressure measure	4906	1808
Participants who completed 48-week follow-up	4617	289
Participants with hypertension at baseline	3809	808
Final sample size	3809	--

### HTN definition

- average systolic blood pressure (SBP)  $\geq$  140 mm Hg
- average diastolic blood pressure (DBP)  $\geq$  90 mm Hg
- initiation of antihypertensive medication
- diagnosis of hypertension

# Baseline Characteristics

	<b>Overall (n = 3,809)</b>
<b>Age, in years</b>	37.3 (10.1)
<b>Female gender</b>	20%
<b>BMI, kg/m<sup>2</sup></b>	25.5 (5.3)
<b>Race/ethnicity</b>	
<b>White, non-Hispanic</b>	40%
<b>Black, non-Hispanic</b>	36%
<b>Hispanic/Latino</b>	24%
<b>SBP, in mm Hg</b>	115.3 (11.4)
<b>DBP, in mm Hg</b>	72.7 (8.2)
<b>Current smoking*</b>	37%
<b>Ever intravenous drug use*</b>	8%
<b>CD4 cell count, cells/mm<sup>3</sup></b>	250 (97, 373)
<b>HIV-1 RNA, log<sub>10</sub></b>	4.7 (4.3, 5.1)
<b>eGFR, in mL/min/1.73m<sup>2</sup></b>	107.6 (19.4)
<b>HCV Ab reactive *</b>	7.4%
<b>Diabetes</b>	80 (2.1%)

Data presented as mean values with SD or median with IQR when not normally distributed.

\*Certain studies did not collect data on smoking, IVDA, and HCV status.



# Baseline Characteristics

	Hypertension at Week 48			p-value
	Overall (n = 3,809)	No (n = 3,370)	Yes (n = 439)	
Age, in years	37.3 (10.1)	36.9 (10.0)	40.5 (10.3)	<0.001
Female gender	20%	20%	19%	0.541
BMI, kg/m <sup>2</sup>	25.5 (5.3)	25.2 (5.0)	27.2 (6.6)	<0.001
Race/ethnicity				0.170
White, non-Hispanic	40%	40%	38%	-
Black, non-Hispanic	36%	35%	40%	-
Hispanic/Latino	24%	24%	22%	-
SBP, in mm Hg	115.3 (11.4)	114.5 (11.3)	121.0 (10.7)	<0.001
DBP, in mm Hg	72.7 (8.2)	72.3 (11.3)	76.2 (7.8)	<0.001
Current smoking*	37%	36%	45%	0.001
Ever intravenous drug use*	8%	8%	10%	0.146
CD4 cell count, cells/mm <sup>3</sup>	250 (97, 373)	256 (103, 375)	214 (68, 332)	0.001
HIV-1 RNA, log <sub>10</sub>	4.7 (4.3, 5.1)	4.7 (4.3, 5.1)	4.8 (4.3, 5.2)	0.066
eGFR, in mL/min/1.73m <sup>2</sup>	107.6 (19.4)	108.1 (19.4)	104.4 (19.5)	0.001
HCV Ab reactive *	7.4%	7.1%	9.6%	0.082
Diabetes	80 (2.1%)	65 (1.9%)	15 (3.4%)	0.041

**439 pts (11.5%)  
developed HTN  
by week 48**

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\*Certain studies did not collect data on smoking, IVDA, and HCV status.

# Parameters associated with HTN at 48 weeks

439 pts (11.5%) developed HTN by week 48

	Unadjusted		Adjusted	
	Relative risk (95% CI)	p-value	Relative risk (95% CI)	p-value
<b>Age, per 10 years</b>	<b>1.35 (1.24 – 1.46)</b>	<b>&lt;0.001</b>	<b>1.31 (1.18 – 1.47)</b>	<b>&lt;0.001</b>
<b>BMI, kg/m<sup>2</sup></b>	<b>1.05 (1.04 – 1.06)</b>	<b>&lt;0.001</b>	<b>1.05 (1.03 – 1.07)</b>	<b>&lt;0.001</b>
HIV-1 RNA, log <sub>10</sub>	1.10 (0.97 – 1.24)	0.138	--	
Waist-to-hip ratio <sup>‡</sup>	1.34 (1.16 – 1.55)	<0.001	1.07 (0.89 – 1.27)	0.476
<b>Female sex</b>	<b>0.93 (0.74 – 1.17)</b>	<b>0.542</b>	<b>0.65 (0.46 – 0.91)</b>	<b>0.011</b>
<b>Race/ethnicity</b>				
<b>Black, non-Hispanic</b>	<b>1.17 (0.96 – 1.43)</b>	<b>0.124</b>	<b>1.35 (1.03 – 1.77)</b>	<b>0.031</b>
Hispanic/Latino	0.96 (0.76 – 1.22)	0.756	1.15 (0.86 – 1.55)	0.338
<b>Current smoking</b>	<b>1.38 (1.14 – 1.68)</b>	<b>0.001</b>	<b>1.34 (1.06 – 1.68)</b>	<b>0.013</b>
Intravenous drug use	1.23 (0.92 – 1.65)	0.165	--	
<b>CD4 cell count, cells/mm<sup>3</sup></b>				
<b>200 - &lt; 350</b>	<b>0.78 (0.63 – 0.96)</b>	<b>0.017</b>	<b>0.73 (0.56 – 0.95)</b>	<b>0.020</b>
<b>350 - &lt; 500</b>	<b>0.67 (0.52 – 0.87)</b>	<b>0.003</b>	<b>0.64 (0.46 – 0.89)</b>	<b>0.008</b>
<b>500 and above</b>	<b>0.59 (0.41 – 0.84)</b>	<b>0.004</b>	<b>0.69 (0.46 – 1.02)</b>	<b>0.063</b>
eGFR < 60mL/min/1.73m <sup>2</sup>	1.62 (1.10 – 2.36)	0.013	1.18 (0.72 – 1.93)	0.510
Hepatitis C	1.33 (0.97 – 1.81)	0.078	1.01 (0.69 – 1.48)	0.948
Diabetes	1.65 (1.04 – 2.62)	0.035	1.14 (0.57 – 2.27)	0.709

Relative risk estimated using modified Poisson regression with robust error variance.

# ARVs associated with HTN at 48 weeks

	Unadjusted		Adjusted <sup>†</sup>	
	Relative risk (95% CI)	p-value	Relative risk (95% CI)	p-value
Drug class				
<b>NNRTI</b>	<b>1.27 (1.06 – 1.51)</b>	<b>0.009</b>	<b>1.29 (1.04 – 1.61)</b>	<b>0.020</b>
NRTI	0.98 (0.66 – 1.46)	0.938	0.93 (0.60 – 1.46)	0.767
<b>PI</b>	<b>0.78 (0.65 – 0.93)</b>	<b>0.006</b>	<b>0.74 (0.56 – 0.91)</b>	<b>0.005</b>
II	0.95 (0.73 – 1.25)	0.738	1.05 (0.76 – 1.44)	0.771

**439 pts (11.5%)  
developed HTN  
by week 48**

-Relative risk estimated using modified Poisson regression with robust error variance.

-Multivariable adjustment for age, gender, and race/ethnicity, CD4 count, HIV – 1 RNA levels, smoking, body mass index, waist-to-hip ratio, eGFR, and diabetes.

# ARVs associated with HTN at 48 weeks

439 pts (11.5%)  
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II	0.95 (0.73 – 1.25)	0.738	1.05 (0.76 – 1.44)	0.771
<b>Individual NRTI</b>				
<b>Abacavir</b>	<b>1.24 (1.06 – 1.54)</b>	<b>0.012</b>	<b>1.27 (1.02 – 1.59)</b>	<b>0.035</b>
<b>Stavudine</b>	<b>2.09 (1.45 – 2.99)</b>	<b>&lt;0.001</b>	<b>1.86 (1.17 – 2.96)</b>	<b>0.009</b>
AZT	1.07 (0.84 – 1.35)	0.600	1.08 (0.84 – 1.40)	0.536
<b>Tenofovir/TDF</b>	<b>0.76 (0.64 – 0.91)</b>	<b>0.002</b>	<b>0.78 (0.62 – 0.97)</b>	<b>0.025</b>
FTC	0.97 (0.66 – 1.43)	0.883	0.93 (0.61 – 1.43)	0.746
<b>Individual PI</b>				
Lopinavir	1.08 (0.81 – 1.44)	0.601	1.07 (0.75 – 1.51)	0.714
<b>Ritonavir</b>	<b>0.75 (0.62 – 0.90)</b>	<b>0.002</b>	<b>0.69 (0.55 – 0.87)</b>	<b>0.002</b>
Nelfinavir	1.09 (0.17 – 6.81)	0.929	0.81 (0.15 – 4.21)	0.800
<b>Darunavir</b>	<b>0.61 (0.43 – 0.85)</b>	<b>0.003</b>	<b>0.65 (0.42 – 0.98)</b>	<b>0.042</b>
Atazanavir	0.89 (0.73 – 1.08)	0.231	0.89 (0.61 – 1.01)	0.057
<b>Individual NNRTI</b>				
<b>Efavirenz</b>	<b>1.28 (1.07 – 1.53)</b>	<b>0.007</b>	<b>1.28 (1.03 – 1.59)</b>	<b>0.027</b>
<b>Individual INSTI</b>				
Raltegravir	0.95 (0.73 – 1.25)	0.738	1.05 (0.76 – 1.44)	0.771

-Relative risk estimated using modified Poisson regression with robust error variance.

-Multivariable adjustment for age, gender, and race/ethnicity, CD4 count, HIV RNA levels, smoking, body mass index, waist-to-hip ratio, eGFR, and diabetes.

# Summary

- HTN is a common comorbidity in the setting of HIV infection and ART initiation
  - 808/4617 (17.5%) had HTN at time of presentation for HIV treatment
  - 439/3809 (11.5%) diagnosed with HTN by week 48 develop HTN
- Certain ARVs are associated with development of HTN
  - NNRTIs (efavirenz)
  - Abacavir
  - Thymidine analogs (d4T)
- Certain ARVs are associated with lower risk of developing HTN
  - TDF
  - Protease inhibitors
- Lower CD4 at time of ART initiation was associated with development of HTN
- Traditional risk factors play a prominent role in development of HTN
  - Age, BMI, male sex, black race, current smoking, H/O diabetes
- Next steps
  - Time updated analysis
  - Look at effect of development of HTN on ART on kidney function
    - longitudinal data on serum Cr and urine protein available



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  - Tony Moore
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  - Heather Ribaudó
  - Christina Wyatt
  - Dustin Long
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  - Mike Saag

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## Results: HTN after ART Initiation

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Proportion of Hypertension at Annual Visits

