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Impact of Antiretroviral Drugs on Hypertension in HIV-positive Persons: D:A:D Study

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BACKGROUND

- The prevalence of hypertension may be higher in HIV-positive (HIV+) compared to HIV-negative individuals (1,2).
- Previous studies have documented that hypertension in HIV+ individuals is associated with traditional risk factors such as older age, male gender, diabetes, dyslipidemia and high body mass index (BMI) (3). However, controversy remains as to whether the exposure to antiretroviral (ARV) drugs poses additional risk (4,5).

STUDY OBJECTIVE

To investigate whether ARV drugs pose additional risk for hypertension in HIV+ individuals in the D:A:D Study.

METHODS

- The D:A:D Study is an observational study of >49,000 HIV+ individuals from 11 cohorts across Europe, Australia and the USA. The primary aim of the study is to investigate potential associations between the use of ARV drugs and cardiovascular disease (CVD) and other clinical events.
- Data are collected prospectively during routine clinic visits and include information on socio-demographic factors, AIDS events and deaths, known risk factors for CVD, laboratory markers for monitoring of HIV and CVD, ARV drugs and treatments that influence CVD and CVD risk.

STATISTICAL METHODS

- Follow-up was from individual study enrolment until the earliest of confirmed hypertension, 6 months after last visit or 1/2/2013. Hypertension was defined as the earliest of the events presented in **Table 1.**
- The incidence of hypertension of individuals with a normal blood pressures (BP) at study entry was determined overall and in various strata defined by demographic, metabolic- and HIV-related factors, including cumulative exposure (/year) to individual ARV drugs. Individuals with no data on BP, pre-existing hypertension and/or on anti-hypertensive treatment at study entry or <2 systolic or diastolic measurements over the follow-up period were excluded from analyses (n=16,439).
- Predictors of hypertension were identified using uni- and multivariable Poisson regression models. The multivariable models were adjusted for the following potential confounders:
  - *Time fixed: Gender, participating cohort, ethnicity, mode of HIV-acquisition*
  - *Time updated (not on the causal pathway): Calendar year, age, smoking status and previous AIDS diagnosis, HIV-RNA viral load, CD4 count, ARV drugs*
  - *Time-updated (on the causal pathway): Total cholesterol (TC), triglycerides (TG), use of lipid-lowering drugs (LLDs), lipodystrophy, BMI, diabetes and estimated glomerular filtration rate (eGFR)*

Table 1 **Definitions of hypertension used in the study**

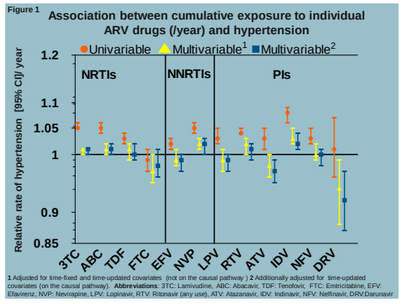
First of any event over follow-up > 6 months	Date taken
• Two consecutive measurements of SBP >140 mmHg	Date of first SBP>140
• Two consecutive measurements of DBP >90 mmHg	Date of first DBP>90
• Single measurement of SBP >140 mmHg followed by measurement of SBP≤140 mmHg, but where ACEI/anti-hypertensive drugs are known to have been initiated between the two measurements	Date of first SBP>140
• Single measurement of DBP >90 mmHg followed by measurement of DBP ≤90 mmHg, but where ACEI/anti-hypertensive drugs are known to have been initiated between the two measurements	Date of first DBP>90
• Single measurement of SBP >140 mmHg, no further measurements, initiation of ACEI/anti-hypertensives within subsequent 6 months	Date of first SBP>140
• Single measurement of DBP >90 mmHg, no further measurements, initiation of ACEI/anti-hypertensives within subsequent 6 months	Date of first DBP>90
• Initiation of ACEI/anti-hypertensives in absence of a high SBP or DBP measurement	Date of initiation of ACEI/anti-hypertensives

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, ACEI: Angiotensin Converting Enzyme Inhibitor

Table 2 **Baseline characteristics of 33,278 persons at D:A:D Study entry**

Demographic and metabolic factors		n	%
Male gender		24,031	72.2
Age (years)	Median (IQR)	38	(32, 44)
Ethnicity			
	White	17,394	52.3
	Black African	2,265	6.8
	Other	753	2.3
BMI (kg/m²)	<18	1,184	3.6
	≥18, <26	24,364	73.2
	>26, ≤30	4,181	12.6
	>30	1,187	3.6
Smoking	Current smoker	14,247	42.8
	Ex-smoker	5,832	17.5
	Never smoker	9,609	28.9
Lipodystrophy		5,960	17.9
Diabetes		662	2.0
Total cholesterol (mmol/l)	Median (IQR)	4.8	(4.0, 5.7)
Triglycerides (mmol/l)	Median (IQR)	1.5	(1.0, 2.4)
HIV-related factors		**n**	**%**
Mode of acquisition	MSM	14,516	43.6
	IDU	5,364	16.1
	Heterosexual	11,409	34.3
AIDS		7,480	22.5
CD4 count (cells/mm³)	Median (IQR)	429	(272, 616)
HIV RNA (log_{10} copies/ml)	Median (IQR)	2.5	(1.7, 4.2)
Ever received ART		22,771	68.4

Figure 1 **Association between cumulative exposure to individual ARV drugs (/year) and hypertension**



1 Adjusted for time-fixed and time-updated covariates (not on the causal pathway) 2 Additionally adjusted for time-updated covariates (on the causal pathway). **Abbreviations**: 3TC: Lamivudine, ABC: Abacavir, TDF: Tenofovir, FTC: Emtricitabine, EFV: Efavirenz, NVP: Nevirapine, LPV: Lopinavir, RTV: Ritonavir (any use), ATV: Atazanavir, IDV: Indinavir, NFV: Nelfinavir, DRV:Darunavir

RESULTS

- Baseline characteristics of individuals at the time of D:A:D Study entry are shown in **Table 2.**
- Of 33,278 included persons, 7636 (22.9%) developed hypertension over 223,149 person years (PYRS) (rate: 3.42 [95% CI 3.35-3.50]/100 PYRS).
- In univariable analyses, there were significant associations between cumulative exposure (/year) to almost all ARV drugs and the risk of hypertension. When adjusting for demographic- and HIV-related factors as well as smoking, only abacavir, nevirapine, ritonavir and indinavir were significantly associated with an increased risk of hypertension. However, these effects were small and were similar when additionally adjusting for metabolic factors potentially on the causal pathway (**Figure 1**).
- The most important other HIV-related factors independently associated with an increased risk of hypertension are displayed in **Figure 2** and were; Mode of HIV acquisition via injection drug use (IDU), previous AIDS diagnosis and a CD4 count < 200 cells/mm³. Conversely, an increasing HIV-RNA viral load was associated with a decreased risk of hypertension.
- The most important demographic and metabolic factors independently associated with a significantly increased rate of hypertension in multivariable models are shown in **Figure 3.**

CONCLUSION

- In this study, we did not find evidence for any strong or clinically relevant independent association between exposure to any of the investigated ARV drugs and the risk of hypertension.
- As previously documented, established and traditional risk factors for hypertension in the general population were also confirmed for the HIV+ population in the D:A:D Study. In addition to demographic and metabolic risk factors, some HIV-related factors such as mode of HIV-acquisition and low CD4 count were also significantly associated with an increased risk of hypertension. We do not have any clear explanation for the independent association between an increasing HIV-RNA viral load and decreased risk of hypertension.
- Our findings provide reassurance that screening policies and preventive measures for hypertension in HIV+ persons should follow the algorithms used for the general population. However, continued pharmacovigilance is warranted for newer ARV drugs not investigated in this study.

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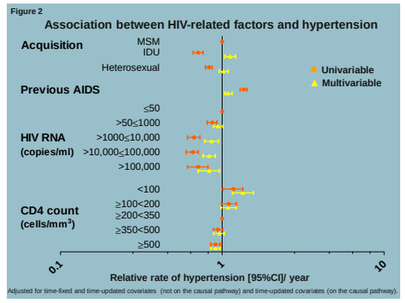
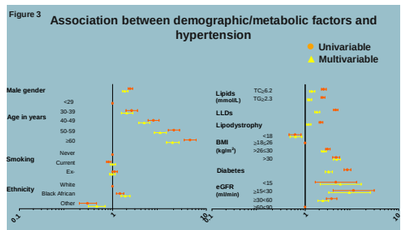
Figure 2 **Association between HIV-related factors and hypertension**



Adjusted for time-fixed and time-updated covariates (not on the causal pathway) and time-updated covariates (on the causal pathway).

Figure 3 **Association between demographic/metabolic factors and hypertension**



Adjusted for time-fixed and time-updated covariates (not on the causal pathway) and time-updated covariates (on the causal pathway).

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