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Association between exposure to antiretroviral drugs and the incidence of hypertension in HIV-positive persons: the D:A:D Study

Running head: Antiretroviral drugs and hypertension

Camilla Ingrid Hatleberg[1], Lene Ryom[1], Antonella d'Arminio Monforte[2], Eric Fontas[3], Peter Reiss[4], Ole Kirk[1], Wafaa El-Sadr[5], Andrew Phillips[6], Stephane de Wit[7], Francois Dabis[8], Rainer Weber[9], Matthew Law[10], Jens Dilling Lundgren[1], Caroline Sabin[6]

On behalf of the Data collection of Adverse events of anti-HIV Drugs (D:A:D) Study Group

Affiliations:

[1] CHIP, Dept. of Infectious Diseases Section 2100, Finsencentret, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;

[2] Dipartimento di Scienze della Salute, Clinica di Malattie Infettive e Tropicali, Azienda Ospedaliera-Polo Universitario San Paolo, Milan, Italy;

[3] Dept. of Public Health, Nice University Hospital, Nice, France;

[4] Academic Medical Center, Dept. of Global Health and Div. of Infectious Diseases, University of Amsterdam, and HIV Monitoring Foundation, Amsterdam, The Netherlands;

[5] ICAP-Columbia University and Harlem Hospital, New York, USA;

[6]Research Dept. of Infection and Population Health, UCL, London, United Kingdom;

[7] Div. of Infectious Diseases, Saint Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium;

[8] CHU de Bordeaux and INSERM U897, Université de Bordeaux, Talence, France;

[9] Division of infectious diseases and hospital epidemiology, University hospital Zurich, University of Zurich, Switzerland;

[10] Kirby Institute, UNSW Sydney, Sydney, Australia

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Corresponding author and reprints:

Camilla Ingrid Hatleberg, MD

CHIP, Dept. of Infectious Diseases, Rigshospitalet,

Blegdamsvej 9,

DK-2100 Copenhagen

Tel: + 45 35 45 57 70/ Fax: +45 35 45 57 57

email: Camilla.hatleberg@regionh.dk

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Short summary of article's main points: This article presents findings indicating that cumulative exposure to antiretroviral drugs is not associated with a clinically relevant increased risk of

hypertension in HIV-positive individuals. Increased risk of hypertension is mainly linked to traditional cardiovascular disease risk factors.

Abstract

Objectives: Previous studies have suggested that hypertension in HIV-positive individuals is associated primarily with traditional risk factors such as older age, diabetes and dyslipidemia. However, controversy remains as to whether exposure to antiretroviral (ARV) drugs poses additional risk, and we investigated this question in the D:A:D cohort.

Methods: The incidence of hypertension (systolic blood pressure (BP) $\geq$140 and/or diastolic BP $\geq$90 mmHg and/or initiation of antihypertensive treatment) was determined overall and in strata defined by demographic, metabolic- and HIV-related factors, including cumulative exposure to each individual ARV drug. Predictors of hypertension were identified using uni- and multivariable Poisson regression models.

Results: Of 33,278 included persons, 7636 (22.9%) developed hypertension over 223,149 person years (Incidence rate: 3.42 [95% CI 3.35-3.50]/100 PYRS). In univariable analyses, cumulative exposure to most ARV drugs was associated with an increased risk of hypertension. After adjustment for demographic, metabolic and HIV-related factors, only associations for nevirapine (rate ratio 1.07 [95% CI 1.04-1.13]/5 years) and indinavir/ritonavir (1.12 [1.04-1.20]/5 years) remained statistically significant, although effects were small. The strongest independent predictors of hypertension were male gender, older age, black African ethnicity, diabetes, dyslipidemia, use of lipid-lowering drugs, high BMI, renal impairment and a low CD4 count.

Conclusion: We did not find evidence for any strong independent association between exposure to any of the individual ARV drugs and the risk of hypertension. Findings provide reassurance that screening policies and preventative measures for hypertension in HIV-positive persons should follow algorithms used for the general population.

INTRODUCTION

Over the last two decades, cardiovascular disease (CVD) has emerged as a leading cause of morbidity and mortality in HIV-positive (HIV+) individuals [1 -3]. The increased prevalence of CVD is a consequence of increased life expectancy resulting from the widespread use of effective combination antiretroviral therapy (cART) [1-3], high prevalence of traditional CVD risk factors (including hypertension) [4-6] and contribution by HIV-related factors [7-9].

The prevalence of hypertension is higher in HIV+ than HIV-negative (HIV-) individuals [10, 11], and is increasing [12]. Hypertension in HIV+ individuals has been linked to traditional CVD risk factors such as diabetes, renal impairment, older age, male gender, black African ethnicity, dyslipidemia and high body mass index (BMI) [12-16]. Furthermore, factors related to HIV, such as immunosuppression, inflammation, increased arterial stiffness, fat redistribution and lipodystrophy may also contribute to an increased risk of hypertension [17-20].

Controversy remains as to whether exposure to antiretroviral (ARV) drugs poses an additional risk for the development of hypertension. Whilst some studies have reported an increased risk of hypertension in those exposed to cART overall [21-25], others have not observed any such association [12, 13, 26-29]. A previous analysis from the Data on Adverse events of antiretroviral Drugs (D:A:D) Study in 2005 showed no clear association between exposure to ARV drugs and the risk of hypertension, although traditional CVD risk factors were significant predictors of hypertension [13].

Given the increased life expectancy of people living with HIV, it is important to continuously improve our understanding of CVD risk factors so as to recommend appropriate preventative measures. Our aim was to capitalize on the additional follow-up that is now available in the D:A:D

study to re-investigate the potential associations between exposure to individual ARV drugs and the risk of hypertension, as well as to identify non-ARV predictors of hypertension.

MATERIAL AND METHODS

Material

The D:A:D Study is an observational, multinational cohort collaboration including >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 ARV drugs and CVD and other clinical events. Data are collected prospectively during routine clinic visits; the dataset includes information on demographic factors, AIDS events and deaths, known risk factors for CVD including blood pressure (BP), laboratory markers for monitoring HIV and CVD, ARV drugs and treatments that influence CVD and CVD risk.

Definition of hypertension

Hypertension was defined to have occurred on the earliest date of the following events: two consecutive systolic blood pressure (SBP) measurements >140 mmHg and/or diastolic blood pressure (DBP) measurements >90 mmHg [30] (with the date of the first raised measurement taken as the diagnosis date); one single SBP >140 mmHg and/or diastolic DBP >90 mmHg with use of anti-hypertensive drugs or angiotensin converting enzyme inhibitors (ACEIs) within 6 months of this measurement (with the date of the first BP measurement again taken as the diagnosis date); or initiation of anti-hypertensive drugs/ACEIs without a recorded high BP (with the date of initiation taken as the diagnosis date). Blood pressure was measured as part of regular study visits within the participating clinic sites of the participating cohorts.

Statistical methods

Participants were followed from study enrolment (1/1/1999 onwards) to the earliest of i) the date when an individual met the criteria for hypertension, ii) death, iii) 6 months after an individuals' last clinic visit, or iv) 1/2/2013, the administrative censoring date for the present analysis.

Individuals with fewer than 2 SBP or DBP measurements during follow-up (and no initiation of anti-hypertensive drugs or ACEIs), those with less than 6 months of follow-up and those with pre-existing hypertension and/or receiving anti-hypertensive treatment at D:A:D entry were excluded from analyses. The incidence of hypertension was determined in the remaining individuals overall and in strata defined by demographic, metabolic- and HIV-related factors. In particular, strata were defined by levels of cumulative exposure to each of the 18 ARV drugs that were commonly prescribed (stavudine (d4T), didanosine (ddI), zalcitabine (ddC), zidovudine (AZT), lamivudine (3TC), abacavir (ABC), emtricitabine (FTC), tenofovir (TDF), efavirenz (EFV), nevirapine (NVP), lopinavir/ritonavir (LPV/r), ritonavir (RTV), fosamprenavir/ritonavir (fAPV/r), atazanavir (ATV), indinavir/ritonavir (IDV/r), nelfinavir (NFV), saquinavir/ritonavir (SQV/r), darunavir/ritonavir (DRV/r)). Our assessment of cumulative exposure to each drug also included any exposure prior to D:A:D enrolment allowing us to include cumulative exposure to several ARV drugs that are no longer in wide-spread use.

We initially investigated unadjusted associations with incident hypertension using Poisson regression models. As in previous analyses of the study, each individual's follow-up was split into a series of consecutive one-month periods and his/her clinical, immunologic and virologic status at the start of each period was established. Thus, cumulative exposure to each ARV drug was assessed in a time-updated manner in these models.

Predictors of hypertension were then identified using the following staged model-building approach: firstly, we fitted a model that included time-updated covariates for exposure to each of the ARV drugs (each covariate was scaled so that the estimate reflected the association with an additional 5 years of exposure to the drug). We then used a backwards selection process to remove drugs from the model that were not independently associated with hypertension risk (note that this model-building step occurred prior to adjustment for non-ARV confounders); this parsimonious model was then taken forward for confounder-adjustment. The first set of adjustments included both fixed (gender, ethnicity, participating cohort, mode of HIV acquisition) and time-updated (age, smoking status, calendar year and a previous AIDS diagnosis) covariates. None of these factors were considered to lie on the causal pathway between ARV exposure and hypertension development. Next, we additionally included adjustment for metabolic factors (total cholesterol (TC), triglycerides (TG), use of lipid-lowering drugs (LLDs), lipodystrophy, BMI, diabetes and estimated glomerular filtration rate (eGFR)) that were potentially on the causal pathway to investigate whether these factors could mediate any associations (with all covariates being considered as time-updated covariates). Finally, we additionally included adjustment for other HIV-related factors, notably the latest/current HIV-RNA viral load (VL) and CD4 count, both as time-updated covariates.

Sensitivity analyses were conducted in which we restricted the analyses to individuals currently on ARV drugs, and in which we used modified definitions of hypertension that were based on *either* the initiation of anti-hypertensives/ACEIs only, or on the presence of elevated BP measurements only.

RESULTS

Most of the included 33,278 individuals were male (72.2%), the median age was 38 years (interquartile range (IQR) 32, 44), around half (52.3 %) were of white ethnicity and 43.6% were men who had acquired HIV through sex with another man (MSM) (Table 1). Whilst approximately 1 in 5 had a previous AIDS diagnosis, the median CD4 count was 429 (IQR 272, 616) cells/mm^3 and nearly 40% of individuals had an undetectable VL (<50 copies/ml), reflecting a relatively high exposure to ART (68.4%) at study entry. The most prevalent CVD risk factor was smoking: 42.8% and 17.5% were current and ex-smokers, respectively. Whilst only 3.8% were on LLDs and only 2.0% had diabetes, 16.1% had a BMI >26 kg/m^2 and 17.9% had lipodystrophy. The median (IQR) number of assessments of SBP/DBP was 10 (2, 160) with median (IQR) SBP and DBP being 120 (110, 130) and 76 (70, 80), respectively.

Incidence of hypertension

7636 (22.9%) persons developed hypertension over 223,149 person years (PYRS) giving an incidence rate (IR) of 3.42 [95% confidence interval (CI) 3.35-3.50] /100 PYRS. The unadjusted IRs were higher in men than in women, in older people, in those of Black African ethnicity, in those with BMI >30kg/m^2, diabetes, with eGFR <60 mL/min/1.73m^2, or CD4 count <100 cells/mm^3. The IR of hypertension generally increased with longer exposure to each ARV drug (data not shown).

Identification of factors associated with hypertension

In univariable analyses, there were significant associations between cumulative exposure to almost all ARV drugs and the risk of hypertension, except for DRV/r (rate ratio [RR] 1.08 [0.84-1.39]/5 years) and FTC (0.94 [0.86-1.03]/5 years).

In a multivariable analysis that included adjustment for all 18 ARV drugs, 12 of the drugs continued to be independently associated with hypertension and were considered further: 3TC, ABC, TDF, FTC, EFV, NVP, LPV/r, RTV, ATV, IDV/r, NFV and DRV/r (Figure 1). After adjusting for demographic factors not on the causal pathway, only use of ABC (1.06 [1.00-1.11]/5 years), NVP (1.11 [1.05-1.17]/5 years), RTV (1.08 [1.01-1.14]/5 years) and IDV/r (1.16 [1.09-1.25]/5 years) remained significantly associated with an increased risk of hypertension (Figure 1). When additionally adjusting for metabolic factors considered to be on the causal pathway, only use of IDV/r (1.12 [1.04-1.20]/5 years) and NVP (1.08 [1.02-1.14]/5 years) remained significantly associated with an increased risk. These associations were unaffected when also adjusting for the latest VL and CD4 count (Figure 1). Cumulative exposure to EFV (0.92 [0.86-0.97]/5 years), ATV (0.84 [0.76-0.94]/5 years) and DRV/r (0.64 [0.48-0.85)/5 years] were each associated with a reduced risk of hypertension in this model.

Of the factors associated with hypertension in the fully adjusted multivariable model (Tables 2a/b), the highest point estimates were observed for male gender, older age, black African ethnicity, HIV acquisition through IDU, previous AIDS, diabetes, a high TC or TG level, use of LLDs, lipodystrophy, BMI >30 kg/m^2 and a low eGFR. We did not observe any association between current smoking and the risk of hypertension. CD4 <100 cells/mm^3 was the strongest HIV-related predictor of hypertension, whereas a VL >100,000 copies/ml was associated with a decreased risk of hypertension.

Results were consistent in sensitivity analyses restricted to individuals currently on ARV, and when redefining hypertension on the basis of either initiating anti-hypertensives/ACEIs or having elevated BP measurements only.

DISCUSSION

Whilst several studies have investigated the potential association between cART and the risk of hypertension, few have been able to investigate associations with individual ARVs due to limited size and/or follow-up. Using data from a large, heterogeneous cohort with information on a wide range of demographic, metabolic and HIV-related factors, we did not find evidence of any strong associations between specific ARV drugs and an increased risk of hypertension. We did, however, document associations with many of the established risk factors for hypertension in the general population, such as older age, male gender, diabetes, high BMI, black African ethnicity and low eGFR, in addition to severe immunosuppression. Our findings are consistent with previous D:A:D findings [13], although our results are based on a substantially longer duration of follow-up and a wider range of ARV drugs.

Prior studies on hypertension in HIV+ individuals have generally been cross-sectional, and reported conflicting prevalence data [10, 11, 22, 28, 29] compared with the general population. In our current study, the incidence of hypertension was lower than previously reported (3.42 [95% CI 3.35-3.50]/100 PYRS vs. 7.21/100 PYRS) [13], possibly reflecting improved CVD risk factor screening or BP monitoring in line with increased focus on CVD management and awareness of hypertension in HIV+ individuals. In contrast, Okeke et al. observed an increasing IR over time (from 1.68/100 PYRS in 1996 to 5.35/100PYRS in 2013) [12], although this study included a higher proportion of individuals of Black African ethnicity and uninsured participants who may not have had access to preventive CVD care.

Prior studies considering associations between ARV exposure and hypertension have also reported divergent findings, likely due to differences in study design, study populations, the definition of

hypertension and the different range of demographic, metabolic and HIV-related factors available for adjustment. Several studies have demonstrated an increased risk of hypertension with cumulative exposure to ARVs [21-24]; after adjustment, Baekken et al. found that individuals exposed to >5 years of cART had higher rates of hypertension than those of age-, sex- and BMI-matched HIV- controls and ART-naïve HIV+ individuals [21] . Two other studies demonstrated an increased risk of hypertension in those with longer exposure to cART [22, 24], but these studies did not adjust for metabolic factors [22], or eGFR, dyslipidemia or HIV-related factors, respectively [24]. Although these studies demonstrated a potential correlation between cART exposure and hypertension, the explanatory mechanisms are unclear. The ARV effect may be mediated through metabolic side effects such as diabetes, dyslipidemia and body fat changes, which have previously been associated with some ARVs [9, 20, 31-33], or it could be mediated directly through changes to endothelial function; An association between cART and aortic stiffness, a risk factor for hypertension, was observed in individuals treated with protease inhibitors in one study [34], although not in another [19], whereas impaired endothelial function has been associated with ABC [35].

A recent meta-analysis found an association between exposure to cART and an increased risk of hypertension (odds ratio 1.68) [23]. However, this meta-analysis was limited by the small number of included studies and the lack of included multivariable analyses. Nduka et al. used propensity score methods to demonstrate a high probability that the link between cART and increased BP in Sub-Saharan Africa was causal [36]. It is possible that the use of older ARVs is potentially more harmful in the black African population, which has a higher hypertension risk than the white population [37].

Conversely, several studies have demonstrated a lack of an independent association between cumulative exposure to cART and hypertension [12, 20, 26-28]. One study suggested that an increased prevalence of hypertension among cART-treated individuals might be driven through abdominal obesity and d4T-induced peripheral lipoatrophy [20]. Thus, most studies that have demonstrated an association with cART have suggested that this is likely to be a consequence of the metabolic side effects of ARVs.

The lack of association between individual ARVs in our study argues that the effects seen in univariable models were mainly explained by confounding with demographic and metabolic factors. Only two ARVs, NVP and IDV/r, remained associated with a significantly increased risk of hypertension, although the adjusted association was small and of limited clinical relevance. In contrast to previous findings [20], we did not observe an independent association between exposure to d4T and hypertension. This may be due to the fact that lipodystrophy is more inconsistently reported in participating D:A:D cohorts, that our study population may have been at lower risk of lipodystrophy when d4T was being used, or the that restriction of the previous study to individuals aged >45 years [20] may have selected a group of long-term survivors with previous lipodystrophy.

We have recently demonstrated that exposure to DRV/r, one of the newer ARVs, is associated with an increased risk of CVD [38]; the findings of the present study which demonstrate a *reduced* risk of hypertension in those with longer DRV/r exposure, suggest that this CVD association is unlikely to be mediated by hypertension.

The strongest demographic/metabolic predictors of hypertension in our study were male gender, older age, black African ethnicity, diabetes, dyslipidemia, use of LLDs, a high BMI and a low eGFR

consistent with previous findings [12-16]. Current or previous smoking was not found to be a predictor; although smoking is an important risk factor for arteriosclerosis and can cause arterial stiffness which could lead to hypertension, there is limited evidence of a direct causal relationship between smoking and hypertension [39]. This lack of association with smoking has been observed in other studies [12, 20, 21, 28]. Of the HIV-related factors, a CD4 count <100 cells/mm^3 was the strongest predictor. Surprisingly, a high VL was associated with a decreased risk of hypertension, consistent with the direction of association in our previous analyses [13]. Since the majority of participating individuals are on cART, those with a high VL may be individuals who are experiencing difficulties in taking or adhering to cART; these individuals may be less likely to engage regularly with care or BP monitoring, making it harder to diagnose hypertension. Furthermore, individuals with high VLs may also have lower BP due to severe HIV-related illness.

The lack of a direct association with cART in our study provides reassurance that, in addition to preventing immunosuppression by prompt initiation of cART, screening policies and preventive measures used in the general population are also applicable in HIV+ individuals. The SPRINT Study [40] demonstrated that more intensive BP control in high CVD risk individuals which target a systolic BP <120 mmHg rather than <140 mmHg, reduced the incidence of adverse CVD events such as myocardial infarction and stroke [40]. As hypertension is prevalent in HIV+ individuals, it is likely that this more aggressive intervention policy should also be applied to those living with HIV, to identify those eligible for anti-hypertensive and LLD therapy. Finally, other non-pharmacological interventions, such as dietary, lifestyle and smoking cessation advice, use of newer ARVs with improved metabolic profiles and the prompt initiation of cART in newly-infected individuals are also of importance.

Limitations

Some limitations to our study should be acknowledged. BP measurements were not standardized across cohorts, which may introduce variability. Furthermore, errors in BP measurement might lead to an over-or underestimation of hypertension incidence, introducing dilution bias which may lead to erroneous negative findings. However, given the strong associations with traditional risk factors, we do not believe that this can explain a lack of association with the ARV drugs in our study. We did not have a HIV- control group, and we were unable to investigate newer ARVs (integrase or entry inhibitors) due to limited follow-up among individuals exposed to these drugs. While we cannot exclude any potential delayed effects of any of the ARVs, we did not see any evidence to support this. Finally, although we have adjusted for known risk factors for hypertension, we cannot exclude the possibility that our findings are affected by unmeasured or unknown confounders, or residual confounding with ethnicity (information on ethnicity was unavailable for some individuals as collection of the information is prohibited in several participating cohorts). ARVs reported to be associated with metabolic side effects might have been avoided in individuals considered to be at high CVD risk, which may have masked potentially true associations.

CONCLUSION

We did not find evidence for any significant clinically-relevant independent associations between exposure to any of the investigated ARV drugs and hypertension risk, but did confirm the importance of traditional risk factors. Our findings provide reassurance that in addition to preventing immunosuppression in HIV+ individuals, screening policies and preventive measures for hypertension in HIV+ persons should follow the algorithms used for the general population. However, continued pharmaco-vigilance is warranted for newer ARV drugs not investigated in this study.

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D:A:D Participating Cohorts

Aquitaine, France; CPCRA, USA; NICE Cohort, France; ATHENA, The Netherlands; EuroSIDA, Europe; SHCS, Switzerland, AHOD, Australia; HIV-BIVUS, Sweden; St.Pierre Brussels Cohort, Belgium; BASS, Spain, The ICONA Foundation, Italy

D:A:D Steering Committee: Names marked with *, Chair with ¢

Cohort PIs: W El-Sadr* (CPCRA), G Calvo* (BASS), F Bonnet and F Dabis* (Aquitaine), O Kirk* and A Mocroft* (EuroSIDA), M Law* (AHOD), A d'Arminio Monforte* (ICONA), L Morfeldt* (HivBIVUS), C Pradier* (Nice), P Reiss* (ATHENA), R Weber* (SHCS), S De Wit* (Brussels)

Cohort coordinators and data managers: A Lind-Thomsen (coordinator), R Salbøl Brandt, M Hillebreght, S Zaheri, FWNM Wit (ATHENA), A Scherrer, F Schöni-Affolter, M Rickenbach (SHCS), A Tavelli, I Fanti (ICONA), O Leleux, J Mourali, F Le Marec, E Boerg (Aquitaine), E Thulin, A Sundström (HIVBIVUS), G Bartsch, G Thompsen (CPCRA), C Necsoi, M Delforge (Brussels), E Fontas, C Caissotti, K Dollet (Nice), S Mateu, F Torres (BASS), K Petoumenos, A Blance, R Huang, R Puhr (AHOD), K Grønborg Laut, D Kristensen (EuroSIDA)

Statisticians: CA Sabin*, AN Phillips*, DA Kamara, CJ Smith, A Mocroft*

D:A:D coordinating office: CI Hatleberg, L Ryom, A Lind-Thomsen, RS Brandt, D Raben, C Matthews, A Bojesen, AL Grevsen, JD Lundgren*¢

Member of the D:A:D Oversight Committee: B Powderly*, N Shortman*, C Moecklinghoff*, G Reilly*, X Franquet*

D:A:D working group experts:

Kidney: L Ryom, A Mocroft*, O Kirk *, P Reiss*, C Smit, M Ross, CA Fux, P Morlat, E Fontas, DA Kamara, CJ Smith, JD Lundgren *¢

Mortality: CJ Smith, L Ryom, CI Hatleberg, AN Phillips*, R Weber*, P Morlat, C Pradier*, P Reiss*, FWNM Wit, N Friis-Møller, J Kowalska, JD Lundgren*¢

Cancer: CA Sabin*, L Ryom, CI Hatleberg, M Law*, A d'Arminio Monforte*, F Dabis*, F Bonnet*, P Reiss*, FWNM Wit, CJ Smith, DA Kamara, J Bohlius, M Bower, G Fätkenheuer, A Grulich, JD Lundgren*¢

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The current members of the 11 Cohorts are as follows:

ATHENA (AIDS Therapy Evaluation Project Netherlands):

Central coordination: P. Reiss*, S. Zaheri, M Hillebregt, F.W.N.M. Wit;

CLINICAL CENTRES (¤ denotes site coordinating physician) Academic Medical Centre of the University of Amsterdam: J.M. Prins¤, T.W. Kuijpers, H.J. Scherpbier, J.T.M. van der Meer, F.W.N.M. Wit, M.H. Godfried, P. Reiss, T. van der Poll, F.J.B. Nellen, S.E. Geerlings, M. van Vugt, D. Pajkrt, J.C. Bos, W.J. Wiersinga, M. van der Valk, A. Goorhuis, J.W. Hovius, J. van Eden, A.

Henderiks, A.M.H. van Hes, M. Mutschelknauss, H.E. Nobel, F.J.J. Pijnappel, S. Jurriaans, N.K.T. Back, H.L. Zaaijer, B. Berkhout, M.T.E. Cornelissen, C.J. Schinkel, X.V. Thomas. Admiraal De Ruyter Ziekenhuis, Goes: M. van den Berge, A. Stegeman, S. Baas, L. Hage de Looff, D. Versteeg. Catharina Ziekenhuis, Eindhoven: M.J.H. Pronk¤, H.S.M. Ammerlaan, E.S. de Munnik. A.R. Jansz, J. Tjhie, M.C.A. Wegdam, B. Deiman, V. Scharnhorst. Emma Kinderziekenhuis: A. van der Plas, A.M. Weijsenfeld. Erasmus MC, Rotterdam: M.E. van der Ende¤, T.E.M.S. de Vries-Sluijs, E.C.M. van Gorp, C.A.M. Schurink, J.L. Nouwen, A. Verbon, B.J.A. Rijnders, H.I. Bax, M. van der Feltz. N. Bassant, J.E.A. van Beek, M. Vriesde, L.M. van Zonneveld. A. de Oude-Lubbers, H.J. van den Berg-Cameron, F.B. Bruinsma-Broekman, J. de Groot, M. de Zeeuw- de Man, C.A.B. Boucher, M.P.G Koopmans, J.J.A van Kampen, S.D. Pas. Erasmus MC–Sophia, Rotterdam: G.J.A. Driessen, A.M.C. van Rossum, L.C. van der Knaap, E. Visser. Flevoziekenhuis, Almere: J. Brangerꝛ, A. Rijkeboer-Mes, C.J.H.M. Duijf-van de Ven. HagaZiekenhuis, Den Haag: E.F. Schippers¤, C. van Nieuwkoop. J.M. van IJperen, J. Geilings. G. van der Hut. P.F.H. Franck. HIV Focus Centrum (DC Klinieken): A. van Eeden¤. W. Brokking, M. Groot, L.J.M. Elsenburg, M. Damen, I.S. Kwa. Isala, Zwolle: P.H.P. Groeneveld¤, J.W. Bouwhuis, J.F. van den Berg, A.G.W. van Hulzen, G.L. van der Bliek, P.C.J. Bor, P. Bloembergen, M.J.H.M. Wolfhagen, G.J.H.M. Ruijs. Leids Universitair Medisch Centrum, Leiden: , F.P. Kroon¤, M.G.J. de Boer, M.P. Bauer, H. Jolink, A.M. Vollaard, W. Dorama, N. van Holten, E.C.J. Claas, E. Wessels. Maasstad Ziekenhuis, Rotterdam: J.G. den Hollander¤, K. Pogany, A. Roukens, M. Kastelijns, J.V. Smit, E. Smit, D. Struik-Kalkman, C. Tearno, M. Bezemer, T. van Niekerk, O. Pontesilli. Maastricht UMC+, Maastricht: S.H. Lowe¤, A.M.L. Oude Lashof, D. Posthouwer, R.P. Ackens, J. Schippers, R. Vergoossen, B. Weijenberg-Maes, I.H.M. van Loo, T.R.A. Havenith. MCH-Bronovo, Den Haag: E.M.S. Leyten¤, L.B.S. Gelinck, A. van Hartingsveld, C. Meerkerk, G.S. Wildenbeest, J.A.E.M. Mutsaers, C.L. Jansen. MC Slotervaart, Amsterdam: J.W. Mulder, S.M.E.

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IT department and eCRF development: G. Palmer, V. Conte, V. Sapparrart

AHOD (Australian HIV Observational Database, Australia):

Central coordination: M. Law *, K. Petoumenos, R Puhr, R Huang (Sydney, New South Wales).
Participating physicians (city, state): R. Moore, S. Edwards, J. Hoy, K. Watson, N. Roth, H Lau (Melbourne, Victoria); M Bloch, D. Baker, A. Carr, D. Cooper, (Sydney, New South Wales);M O'Sullivan (Gold Coast, Queensland), D. Nolan, G Guelfi (Perth, Western Australia).

BASS (Spain):

Central coordination: G. Calvo, F. Torres, S. Mateu (Barcelona);

Participating physicians (city): P. Domingo, M.A. Sambeat, J. Gatell, E. Del Cacho, J. Cadafalch, M. Fuster (Barcelona); C. Codina, G. Sirera, A. Vaqué (Badalona).

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Participating physicians: N. Clumeck, S. De Wit*, AF Gennotte, M. Gerard, K. Kabeya, D. Konopnicki, A. Libois, C. Martin, M.C. Payen, P. Semaille, Y. Van Laethem.

The Brussels St Pierre Cohort (Belgium):

Coordination: S. De Wit*, N. Clumeck, M. Delforge, C. Necsoi.

Participating physicians: N. Clumeck, S. De Wit*, AF Gennotte, M. Gerard, K. Kabeya, D. Konopnicki, A. Libois, C. Martin, M.C. Payen, P. Semaille, Y. Van Laethem.

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The multi-centre study group, EuroSIDA (national coordinators in parenthesis).

Argentina: (M Losso), M Kundro, Hospital JM Ramos Mejia, Buenos Aires.

Austria: (B Schmied), Pulmologisches Zentrum der Stadt Wien, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck.

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Belgium: (N Clumeck), S De Wit, M Delforge, Saint-Pierre Hospital, Brussels; E Florence, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent.

Bosnia-Herzegovina: (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo.

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Ospedale di Bolzano, Divisione Malattie Infettive, Bolzano, Italy

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Dérer Hospital, Bratislava, Slovakia

Hospital Carlos III, Departamento de Enfermedades Infecciosas, Madrid, Spain

Kiev Centre for AIDS, Kiev, Ukraine

Luhansk State Medical University, Luhansk, Ukraine

Odessa Region AIDS Center, Odessa, Ukraine

HivBivus (Sweden):

Central coordination: L. Morfeldt, G. Thulin, A. Sundström.

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Nice HIV Cohort (France):

Central coordination: C. Pradier*, E. Fontas, K. Dollet, C. Caissotti.

Participating physicians: P. Dellamonica, E. Bernard, J. Courjon, E. Cua, F. De Salvador-Guillouet, J.Durant, C. Etienne, S. Ferrando, V. Mondain-Miton, A. Naqvi, I. Perbost,S. Pillet , B. Prouvost-Keller, P. Pugliese, V. Rio, K. Risso, P.M. Roger.

SHCS (Swiss HIV Cohort Study, Switzerland):

The data are gathered by the Five Swiss University Hospitals, two Cantonal Hospitals,15 affiliated hospitals and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers).

Members of the Swiss HIV Cohort Study:

Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Pantaleo G, Paioni P, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother

& Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R*, Yerly S.

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Authors' contributions

C.I.H, L.R., J.D.L. and C.S. developed the initial analysis protocol. C.I.H and L.R performed study co-ordination and prepared the datasets for analysis, C.S. performed the statistical analysis. C.I.H. prepared the first draft of the manuscript and completed all revisions. L.R, J.D.L and C.S provided critical input at all stages of the preparation of the manuscript. W.E.S, A.P, P.R, S.D.W, F.D, E.F, A.D.M, R.W and M. L provided data and revised the manuscript critically. All authors have provided input at all stages of the project and approved the final version.

Conflicts of interest

Antonella d'Arminio Monforte has received grants for advisory boards or lectures by Abbve, BMS, Gilead, Janssen, MSD, ViiV

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Table 1: Baseline characteristics at the time of D:A:D Study entry for individuals included in analyses

		n	%
Total number of participants		33278	(100.0)
Demographic factors			
Male gender, n (%)		24031	(72.2)
Age (years)	Median (IQR)	38	(32, 44)
Mode of infection, n (%)	MSM	14516	(43.6)
	IDU	5364	(16.1)
	Heterosexual	11409	(34.3)
	Other/not known	1989	(6.0)
Race, n (%)	White	17394	(52.3)
	Black African	2265	(6.8)
	Other	753	(2.3)
	Not known	12866	(38.7)
Duration of follow-up (years)	Median (IQR)	7.6	(4.7, 11.2)
HIV–related factors			
AIDS, n (%)		7480	(22.5)
CD4 count (cells/mm^3)	Median (IQR)	429	(272, 616)
HIV RNA viral load(log_{10} copies/ml)	Median (IQR)	2.5	(1.7, 4.2)
	n (%) $\leq$50 copies/ml	12664	(38.1)
Ever received ART	n (%)	22771	(68.4)
Ever received NRTIs	n (%)	22384	(67.3)
Ever received PIs	n (%)	17223	(51.8)
Ever received NNRTIs	n (%)	11661	(35.0)
Metabolic factors			
BMI (kg/m^2), n (%)	<18	1184	(3.6)
	$\geq$18, $\leq$26	24364	(73.2)
	>26, $\leq$30	4181	(12.6)
	>30	1187	(3.6)
	Not known	2362	(7.1)
Smoking, n (%)	Current smoker	14247	(42.8)

	Ex-smoker	5832	(17.5)
	Never smoker	9609	(28.9)
	Not known	3590	(10.8)
Lipodystrophy, n (%)		5960	(17.9)
Diabetes, n (%)		662	(2.0)
eGFR (mL/min/1.73m^2) (n=13699)		105	(90, 124)
On lipid-lowering drugs, n (%)		1248	(3.8)
Total cholesterol (mmol/l)	Median (IQR)	4.8	(4.0, 5.7)
HDL-cholesterol (mmol/l)	Median (IQR)	1.1	(0.9, 1.4)
Triglycerides (mmol/l)	Median (IQR)	1.5	(1.0, 2.4)
SBP			
Number of measurements	Median (range)	10	(2, 160)
Value (mmHg)	Median (IQR)	120	(110, 130)
DBP			
Number of measurements	Median (range)	10	(2, 160)
Value (mmHg)	Median (IQR)	76	(70, 80)

Abbreviations: MSM: Men who have sex with men; IDU: Intravenous drug use; ART: Antiretroviral therapy; NRTI: Nucleotide reverse transcriptase inhibitors; PI: Protease Inhibitors; NNRTI: Non-nucleoside reverse transcriptase inhibitors; BMI: Body mass index; eGFR: estimated glomerular filtration rate; HDL-cholesterol: high density lipoprotein cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Table 2: Association between hypertension and other risk factors, fully adjusted model*;

a) Demographic and metabolic

Factor		RR	95% CI	p-value
Gender	Male	1.35	(1.27, 1.45)	0.0001
Age (years)	<29	1	-	-
	30-39	1.42	(1.24, 1.64)	0.0001
	40-49	2.18	(1.90, 2.51)	0.0001
	50-59	3.24	(2.80, 3.74)	0.0001
	≥60	4.39	(3.76, 5.13)	0.0001
Smoking status	Current	1.00	(0.94, 1.07)	0.91
	Ex-	0.99	(0.93, 1.06)	0.83
	Never	1	-	-
	Unknown	1.13	(1.03, 1.25)	0.01
Ethnic group	White	1	-	-
	Black African	1.37	(1.23, 1.53)	0.0001
	Other	0.68	(0.55, 0.83)	0.0002
	Unknown	0.87	(0.72, 1.06)	0.17
Mode of HIV acquisition	MSM	1	-	-
	IDU	1.12	(1.04, 1.21)	0.004
	Heterosexual	1.02	(0.96, 1.09)	0.47
	Other/unknown	1.15	(1.04, 1.27)	0.006
TC ≥6.2 mmol/l	Yes	1.18	(1.11, 1.26)	0.0001
TG ≥2.3 mmol/l	Yes	1.11	(1.06, 1.17)	0.0001
Use of lipid-lowering drugs	Yes	1.34	(1.26, 1.43)	0.0001
Lipodystrophy	Yes	1.09	(1.03, 1.15)	0.003
BMI (kg/m^2)	<18	0.79	(0.69, 0.92)	0.002
	≥18, ≤26	1	-	-
	>26, ≤30	1.58	(1.49, 1.68)	0.0001
	>30	2.18	(2.00, 2.38)	0.0001
	Not known	0.96	(0.85, 1.08)	0.48
Diabetes		1.79	(1.63, 1.95)	0.0001
eGFR (mL/min/1.73m^2)	<15	2.39	(1.44, 3.97)	0.0008
	≥15, <30	2.98	(1.79, 4.96)	0.0001
	≥30, <60	1.55	(1.36, 1.77)	0.0001
	≥60, <90	1	-	-
	≥90, <120	0.97	(0.92, 1.03)	0.37
	≥120	0.89	(0.82, 0.97)	0.008

	Unknown	0.96	(0.88, 1.05)	0.35

b) HIV-related

Factor		RR	95% CI	p-value
Previous AIDS diagnosis		1.09	(1.04, 1.15)	0.0005
HIV RNA (copies/ml)	Unknown	0.39	(0.23, 0.65)	0.0003
	≤50	1	-	-
	>50, ≤1000	0.94	(0.88, 1.01)	0.09
	>1000, ≤10,000	0.86	(0.78, 0.95)	0.003
	>10,000, ≤100,000	0.83	(0.76, 0.91)	0.0001
	>100,000	0.83	(0.71, 0.96)	0.01
CD4 count (cells/mm^3)	Missing	0.96	(0.38, 2.41)	0.94
	<100	1.34	(1.16, 1.56)	0.0001
	≥100, <200	1.09	(0.98, 1.22)	0.10
	≥200, <350	1	-	-
	≥350, <500	0.96	(0.89, 1.03)	0.21
	≥500	0.91	(0.85, 0.97)	0.003

Abbreviations: MSM: Men who have sex with men; IDU: Intravenous drug use; TC: Total cholesterol; TG: Triglycerides; BMI: Body mass index; eGFR: estimated glomerular filtration rate.

*Multivariable model adjusted for demographic (gender, age, ethnicity, participating cohort, smoking status, mode of acquisition of HIV, calendar year and a previous AIDS diagnosis); metabolic ((TC), (TG), use of lipid-lowering drugs, lipodystrophy, BMI, diabetes and eGFR and HIV-related variables (CD4 count, HIV-RNA viral load and individual anti-retroviral drugs).

Figure legends

Figure 1: Associations (risk ratios) between individual ARVs and hypertension per 5 years exposure, uni-and multivariable model

● **Univariable** ▲ **Multivariable[1]** ■ **Multivariable[2]**

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) and time-updated CD4 count and HIV-viral load. Abbreviations: 3TC: Lamivudine, ABC: Abacavir, TDF: Tenofovir, FTC: Emtricitabine, EFV: Efavirenz, NVP: Nevirapine, LPV/r: Lopinavir/r, RTV: Ritonavir (any use), ATV: Atazanavir, IDV/r: Indinavir, NFV: Nelfinavir, DRV/r:Darunavir/r

Figure 1: Associations (risk ratios) between individual ARVs and hypertension per 5 years exposure, uni-and multivariable model