Commonly Prescribed Antiretroviral Therapy Regimens and Incidence of AIDS-Defining Neurological Conditions

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Background: The differential effects of commonly prescribed combined antiretroviral therapy (cART) regimens on AIDS-defining neurological conditions (neuroAIDS) remain unknown.

Setting: Prospective cohort studies of HIV-positive individuals from Europe and the Americas included in the HIV-CAUSAL Collaboration.

Methods: Individuals who initiated a first-line cART regimen in 2004 or later containing a nucleoside reverse transcriptase inhibitor backbone and either atazanavir, lopinavir, darunavir, or efavirenz were followed from cART initiation until death, lost to follow-up, pregnancy, the cohort-specific administrative end of follow-up, or the event of interest, whichever occurred earliest. We evaluated 4 neuroAIDS conditions: HIV dementia and the opportunistic infections toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy. For each outcome, we estimated hazard ratios for atazanavir, lopinavir, and darunavir compared with efavirenz via a pooled logistic model.

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Our models were adjusted for baseline demographic and clinical characteristics.

Results: Twenty six thousand one hundred seventy-two individuals initiated efavirenz, 5858 initiated atazanavir, 8479 initiated lopinavir, and 4799 initiated darunavir. Compared with efavirenz, the adjusted HIV dementia hazard ratios (95% confidence intervals) were 1.72 (1.00 to 2.96) for atazanavir, 2.21 (1.38 to 3.54) for lopinavir, and 1.41 (0.61 to 3.24) for darunavir. The respective hazard ratios (95% confidence intervals) for the combined end point were 1.18 (0.74 to 1.88) for atazanavir, 1.61 (1.14 to 2.27) for lopinavir, and 1.36 (0.74 to 2.48) for darunavir. The results varied in subsets defined by calendar year, nucleoside reverse transcriptase inhibitor backbone, and age.

Conclusion: Our results are consistent with an increased risk of neuroAIDS after initiating lopinavir compared with efavirenz, but temporal changes in prescribing trends and confounding by indication could explain our findings.

Key Words: HIV, HIV dementia, antiretroviral therapy, neuroAIDS

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INTRODUCTION

As the life expectancy of individuals living with HIV increases, more research is needed to understand the impact of HIV and combined antiretroviral therapy (cART) on neurodegeneration, cognitive decline, and aging in general.[1–3] Although the incidence of AIDS-defining neurological conditions (neuroAIDS) in high-income countries decreased after the introduction of cART,[4–7] the potential for differential effects of commonly prescribed cART regimens on neuroAIDS has not been well evaluated.

Clinical guidelines for HIV-positive individuals recommend ritonavir-boosted protease inhibitor (bPI)–based regimens[8–10] and nonnucleoside reverse transcriptase inhibitor (NNRTI)–based regimens[10] as first-line regimens in addition to the newer integrase strand transfer inhibitor (InSTI) regimens. Commonly prescribed bPIs include atazanavir, lopinavir, and darunavir and one of the most commonly prescribed NNRTIs is efavirenz. Although recent guidelines have shifted to recommend InSTI regimens over other regimens as first-line regimens, switching from other regimens to InSTI regimens is currently not recommended unless an individual experiences virologic failure or drug-related toxicity. However, switching for regimen simplification, personal preference, or after diagnosis with a comorbidity also occurs. Because cART is life long, many individuals who initiated bPI and NNRTI-based regimens in the cART era could remain on these regimens for the long term.

cART regimens with high penetration into the central nervous system (CNS) more effectively target HIV replication in the brain. Previous studies of the relationship between cART and neuroAIDS have focused on antiretroviral CNS penetration rather than specific drug regimens. These studies have had conflicting results,[7,11–13] and the clinical relevance of the CNS penetration ranking system is questionable.[7] To our knowledge, no studies have compared the effect of different cART regimens on neuroAIDS.

Here, we use data from prospective cohort studies of HIV-positive individuals in Europe and the Americas to investigate the potential effect of commonly prescribed cART regimens on the clinical diagnoses of 4 neuroAIDS conditions: HIV dementia and the opportunistic infections toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy.

METHODS

Study Population

The HIV-CAUSAL Collaboration includes prospective cohort studies from 6 European countries and the Americas.[14] The individual cohort studies are French Hospital Database-ANRSC04 (France), ANRS PRIMO (France), ANRS SERO-CO (France), ANRS CO3-Aquitaine (France), UK CHIC (United Kingdom), UK Register of HIV Seroconverters (United Kingdom), ATHENA (the Netherlands), Swiss HIV Cohort Study (Switzerland), PISCIS (Spain), CoRIS/CoRIS-MD (Spain), GEMES (Spain), VACS (United States), AMACS (Greece), IPEC (Brazil), and Southern Alberta Cohort (Canada). Each cohort was assembled prospectively and is based on data collected for clinical purposes. All cohorts included in the HIV-CAUSAL Collaboration collected data prospectively, including all CD4 cell counts, HIV RNA measurements, treatment initiations, deaths, and AIDS-defining illnesses (including the events of interest).

Our analysis was restricted to previously antiretroviral therapy–naive HIV-positive individuals who initiated a first-line cART regimen in 2004 or later containing a nucleoside reverse transcriptase inhibitor (NRTI) backbone and either boosted atazanavir, boosted lopinavir, boosted darunavir, or efavirenz. Only a small number of individuals started cART with InSTI or a fusion inhibitor and were therefore excluded. Individuals who initiated an NNRTI other than efavirenz, a bPI other than atazanavir, lopinavir, or darunavir, or more than one of the drugs listed previously were also excluded. Our analysis was further restricted to individuals who met the following criteria at the date of cART initiation (baseline): age 18 years or older, no pregnancy (when information was available), no history of AIDS (defined as the onset of any CDC Classification Category C AIDS-defining illness), and CD4 cell count and HIV RNA measured within the previous 6 months. Individuals were required to start all of the drugs in their first-line cART regimen within the same calendar month. Individuals who changed or discontinued antiretroviral therapy remained classified by their initial regimen as would have been done in an intention-to-treat analysis of a randomized trial.

We allowed regimens to be paired with all NRTI backbones in our main analysis but restricted the analysis to NRTI backbones appearing in the most recent guidelines in subgroup analyses. Specifically, we focused on the backbones abacavir/lamivudine, tenofovir/emtricitabine, and tenofovir/lamivudine.

TABLE 1. Characteristics of 45,308 Antiretroviral Therapy–Naive HIV-Positive Individuals at Baseline by the Type of Initial cART Regimen, HIV-CAUSAL Collaboration, 2004–2015

Characteristic	Efavirenz (n = 26,172)	Atazanavir (n = 5858)	Lopinavir (n = 8479)	Darunavir (n = 4799)
Sex				
Men	22,442 (85.8)	4640 (79.2)	5920 (69.8)	4087 (85.2)
Women	3730 (14.3)	1218 (20.8)	2559 (30.2)	712 (14.8)
Age, yr				
<35	9146 (35.0)	1964 (33.5)	3133 (37.0)	1710 (35.6)
35–50	12,175 (46.5)	2746 (46.9)	3895 (45.9)	2212 (46.1)
>50	4851 (18.5)	1148 (19.6)	1451 (17.1)	877 (18.3)
Geographic origin				
Western countries	13,542 (51.7)	3572 (61.0)	5082 (59.9)	3026 (63.1)
Sub-Saharan Africa	1439 (5.5)	507 (8.7)	1342 (15.8)	336 (7.0)
Other	2786 (10.6)	523 (8.9)	831 (9.8)	403 (8.4)
Unknown	8405 (32.1)	1256 (21.4)	1224 (14.4)	1034 (21.6)
Acquisition group				
Heterosexual	7621 (29.1)	1985 (33.9)	3972 (46.9)	1345 (28.0)
Homosexual	12,808 (48.9)	2500 (42.7)	2797 (33.0)	2699 (56.2)
Injection drug use	688 (2.6)	262 (4.5)	545 (6.4)	197 (4.1)
Other/unknown*	5055 (19.3)	1111 (19.0)	1165 (13.7)	558 (11.6)
CD4 cell count, per mm^3				
<200	8108 (31.0)	1870 (31.9)	4057 (47.9)	1481 (30.9)
200–299	7488 (28.6)	1524 (26.0)	2026 (23.9)	908 (18.9)
300–399	5951 (22.7)	1295 (22.1)	1203 (14.2)	1032 (21.5)
≥400	4625 (17.7)	1169 (20.0)	1193 (14.1)	1378 (28.7)
HIV RNA, copies/mL				
<10,000	4682 (17.9)	1105 (18.9)	1512 (17.8)	720 (15.0)
10,000–100,000	11,776 (45.0)	2571 (43.9)	3102 (36.6)	1825 (38.0)
>100,000	9714 (37.1)	2182 (37.3)	3865 (45.6)	2254 (47.0)
Race				
White	6464 (24.7)	1344 (22.9)	1474 (17.4)	1577 (32.9)
Black	2484 (9.5)	400 (6.8)	555 (6.6)	258 (5.4)
Other/unknown	17,224 (65.8)	4114 (70.2)	6450 (76.1)	2964 (61.8)
Years since HIV diagnosis				
	12,660 (48.4)	2737 (46.7)	5114 (60.3)	2809 (58.5)
<1				
1–4	7798 (29.8)	1649 (28.2)	1767 (20.8)	964 (20.1)
≥5 or unknown	5714 (21.8)	1472 (25.1)	1598 (18.9)	1026 (21.4)
Calendar yr				
2004–2007	8186 (31.3)	1512 (25.8)	4787 (56.5)	22 (0.5)
≥2008	17,986 (68.7)	4346 (74.2)	3692 (43.5)	4777 (99.5)
Cohort				
UK CHIC	7254 (27.7)	1079 (19.4)	905 (10.7)	825 (17.2)
ATHENA	3479 (13.3)	572 (9.8)	677 (8.0)	520 (10.8)
FHDH-ANRS CO4	3144 (12.0)	1668 (28.5)	3175 (37.5)	1095 (22.8)
Aquitaine	231 (0.9)	107 (1.8)	253 (3.0)	57 (1.2)
SHCS	1071 (4.1)	356 (6.1)	486 (5.7)	442 (10.4)
PISCIS/AMACS	2661 (10.2)	639 (10.9)	1108 (13.1)	499 (10.4)
CoRIS	2751 (10.5)	353 (6.0)	755 (8.9)	568 (11.8)
Seroconverters†	785 (3.0)	183 (3.1)	280 (3.3)	463 (9.7)
VACS-VC	3509 (13.4)	745 (12.7)	525 (6.2)	226 (4.7)
IPEC	985 (3.8)	126 (2.2)	112 (1.3)	0 (0)
SAC	302 (1.2)	30 (0.5)	203 (2.4)	104 (2.2)

*Other/unknown acquisition group included all VACS-VC participants.
†Includes the UK Register of HIV seroconverters, ANRS PRIMO, and GEMES (Grupo Español Multicéntrico para el Estudio de Seroconvertores-Hemofilia) cohorts.

We conducted separate analyses for HIV dementia, toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy. Because the opportunistic infections were relatively rare and some mechanisms through which cART regimens may affect opportunistic infections could overlap, we also considered a combined end point of any of the 3 opportunistic infections. The date of neuroAIDS was identified by the treating physicians. One of the contributing cohorts (VACS) used *International Classification of Diseases, Ninth Revision* codes to identify incident neuroAIDS cases. The other contributing cohorts used diagnostic procedures that reflect standard clinical practice rather than standardized research criteria. Non-Hodgkin lymphoma was not included as an outcome because in most cases, it was not possible to differentiate primary brain lymphoma from other types of non-Hodgkin lymphoma. Other HIV-associated neurocognitive disorders, including mild neurocognitive disorder and asymptomatic neurocognitive impairment, were not included because this information was not usually recorded in the medical records. Individuals were followed from baseline until death, 12 months after the most recent laboratory measurement, pregnancy (if known), the cohort-specific administrative end of follow-up (ranging from December 2009 to November 2015), or the event of interest, whichever occurred first.

Statistical Methods

We used a pooled logistic regression model to estimate neuroAIDS hazard ratios for each cART regimen versus efavirenz. A separate model was fit for each neuroAIDS condition and for the combined end point. The model included an indicator for the cART regimen, month of follow-up (restricted cubic splines with 4 knots at 1, 6, 24, and 60 months), and the following covariates at cART initiation: CD4 cell count (<200, 200–299, 300–399, ≥400 cells/μL), HIV-RNA (<10,000, 10,000–100,000, >100,000 copies/mL), sex, race (white, black, other or unknown), geographic origin (Western countries, sub-Saharan Africa, other, or unknown), calendar year (2004–2007, ≥2008), mode of HIV acquisition (heterosexual, homosexual/bisexual, injection drug use, other or unknown), years since HIV diagnosis (<1, 1–4, ≥5 years or unknown), cohort region, and age (<35, 35–49, ≥50 years).

We performed several subset and sensitivity analyses. We restricted our analyses to individuals initiating cART in 2008 or later, to individuals aged 50 years or younger at cART initiation, to individuals with CD4 cell count less than or equal to 400 cells per microliter at cART initiation, to individuals diagnosed with HIV within the previous 5 years, to individuals from western countries, to men, and to those whose acquisition group was other than injection drug use. Because individuals who were lost to follow-up might be different from those who remained in the study, we used inverse probability weighting to adjust for potential selection bias because of infrequent laboratory measurements. Each patient received a time-varying weight inversely proportional to the estimated probability of not being censored, for each

TABLE 2. NeuroAIDS Outcomes for Regimens Based on Atazanavir, Lopinavir, and Darunavir Versus Efavirenz, HIV-CAUSAL Collaboration 2004–2015

NeuroAIDS Event	Treatment	Person-yr	No. Events	Unadjusted Hazard Ratio	95% CI	Adjusted Hazard Ratio†	95% CI
HIV dementia	Efavirenz	100,979	49	1.00	Reference	1.00	Reference
	Atazanavir	19,010	19	1.79	1.05 to 3.05	1.72	1.00 to 2.96
	Lopinavir	36,298	38	2.90	1.83 to 4.59	2.21	1.38 to 3.54
	Darunavir	9680	7	1.40	0.62 to 3.18	1.41	0.61 to 3.24
Opportunistic infections*	Efavirenz	100,803	90	1.00	Reference	1.00	Reference
	Atazanavir	18,968	22	1.09	0.68 to 1.73	1.18	0.74 to 1.88
	Lopinavir	36,190	76	2.39	1.73 to 3.28	1.61	1.14 to 2.27
	Darunavir	9674	13	0.96	0.54 to 1.72	1.36	0.74 to 2.48
Toxoplasmosis	Efavirenz	100,987	40	1.00	Reference	1.00	Reference
	Atazanavir	19,003	9	0.95	0.47 to 1.91	1.11	0.54 to 2.26
	Lopinavir	36,314	34	2.05	1.27 to 3.30	1.41	0.84 to 2.37
	Darunavir	9683	6	0.86	0.37 to 1.99	1.27	0.52 to 3.06
Cryptococcal meningitis	Efavirenz	101,033	26	1.00	Reference	1.00	Reference
	Atazanavir	19,038	4	0.71	0.25 to 2.07	0.73	0.25 to 2.17
	Lopinavir	36,392	14	1.78	0.91 to 3.47	1.21	0.59 to 2.45
	Darunavir	9690	2	0.78	0.18 to 3.32	1.28	0.28 to 5.92
Progressive multifocal leukoencephalopathy	Efavirenz	100,990	26	1.00	Reference	1.00	Reference
	Atazanavir	19,017	10	1.78	0.85 to 3.73	1.84	0.88 to 3.83
	Lopinavir	36,387	28	3.18	1.83 to 5.51	2.16	1.17 to 3.98
	Darunavir	9684	5	1.16	0.44 to 3.09	1.46	0.54 to 3.93

*Includes toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy.
†Adjusted for the baseline covariates (sex, age, race, geographic origin, mode of transmission, CD4 cell count, HIV RNA, calendar year, and years since HIV diagnosis).

month that patient was followed. To estimate the weights, we fit a pooled logistic model using the baseline covariates listed above and the most recent measurement of the time-varying covariates: CD4 cell count (restricted cubic splines with 5 knots at 10, 200, 350, 500, and 1000 cells/μL), HIV RNA (<10,000, 10,000–100,000, >100,000 copies/mL), time since last laboratory measurement (0, 1–2, 3–4, 5–6, >6 months), and AIDS.[15,16] We also weighted by the inverse probability of remaining alive as a sensitivity analysis for competing risks.[17] Finally, we excluded efavirenz regimens from the analysis because individuals initiating efavirenz regimens may be different than individuals initiating other regimens in ways related to the outcomes and compared lopinavir and darunavir regimens with atazanavir regimens.

All analyses were conducted with SAS 9.4 (SAS Institute, Cary, NC).

Ethical Approval

Research using the HIV-CAUSAL Collaboration was determined to be nonhuman subjects research by the Institutional Review Board of the Harvard T.H. Chan School of Public Health because it involves the study of existing data that is analyzed in such a manner that the subjects cannot be identified, as set forth in US federal regulations. Written informed consent from patients was not required because all data were completely anonymized.

RESULTS

Of 45,308 individuals who initiated cART in 2004 or later, 26,172 initiated an efavirenz regimen, 5858 initiated an atazanavir regimen, 8479 initiated a lopinavir regimen, and 4799 initiated a darunavir regimen. Compared with efavirenz, atazanavir, and darunavir, those initiating lopinavir had lower baseline CD4 cell counts and were more likely to be women, have heterosexual sex as their mode of HIV acquisition, and have initiated cART before 2008 (Table 1). The median [interquartile range (IQR)] baseline CD4 cell count at cART initiation was 208 (106–291) cells per microliter among individuals initiating cART before 2008 and 270 (170–358) cells per microliter among individuals initiating cART in 2008 or later.

Over the follow-up period, there were 113 cases of HIV dementia, 201 cases of the combined end point of any neuroAIDS opportunistic infection, 89 cases of toxoplasmosis, 46 cases of cryptococcal meningitis, and 69 cases of progressive multifocal leukoencephalopathy. Sixteen

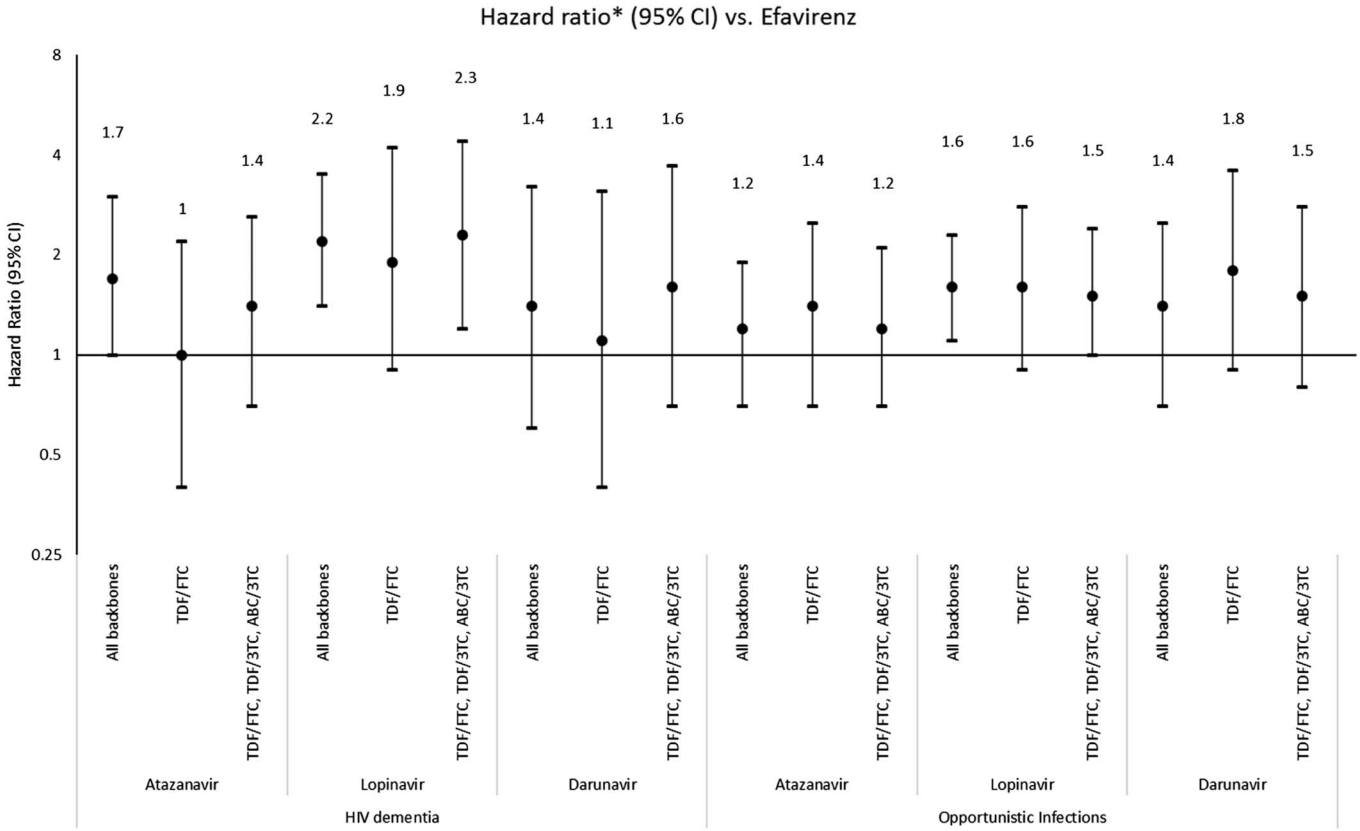

FIGURE 1. NeuroAIDS outcomes by recommended NRTI backbone, HIV-CAUSAL Collaboration 2004–2015. *Adjusted for the baseline covariates (sex, age, race, geographic origin, mode of transmission, CD4 cell count, HIV RNA, calendar year, and years since HIV diagnosis). 3TC, lamivudine; ABC, abacavir; FTC, emtricitabine; TDF, tenofovir; Full results in Supplemental Digital Content Table 1, http://links.lww.com/QAI/B87 and Supplemental Digital Content Figure 1, http://links.lww.com/QAI/B87.

individuals developed 2 of the 4 neuroAIDS conditions and 1 individual developed 3. The median (IQR) follow-up time was 37 (20–64) months in the HIV dementia analysis and was similar in the other analyses. Among those with the event, the median (IQR) time to event ranged from 3 (1–7) months for progressive multifocal leukoencephalopathy to 8 (2–23) months for HIV dementia. Compared with efavirenz, the HIV dementia hazard ratios [95% confidence intervals (CIs)] were 1.72 (1.00 to 2.96) for atazanavir, 2.21 (1.38 to 3.54) for lopinavir, and 1.41 (0.61 to 3.24) for darunavir. Compared with efavirenz, the hazard ratios (95% CIs) for the combined end point were 1.18 (0.74 to 1.88) for atazanavir, 1.61 (1.14 to 2.27) for lopinavir, and 1.36 (0.74 to 2.48) for darunavir. The hazard ratios (95% CIs) comparing each cART regimen with efavirenz for the individual opportunistic infections were close to 1.00 for toxoplasmosis and cryptococcal meningitis, but ranged from 1.46 (0.54 to 3.93) (darunavir) to 2.16 (1.17 to 3.98) (lopinavir) for progressive multifocal leukoencephalopathy (Table 2). In general, these hazard ratios were attenuated compared with the unadjusted estimates. For the combined end point, the median (IQR) CD4 cell count at the time of event was 134 (52, 266) cells per microliter for atazanavir, 72 (29, 161) cells per microliter for efavirenz, 75 (30, 190) cells per microliter for lopinavir, and 108 (49, 179) cells per microliter for darunavir.

Figure 1 compares the neuroAIDS hazard ratios estimated for all NRTI backbones with those estimated when the analysis was restricted to tenofovir/emtricitabine backbones and any of the following NRTI backbones: tenofovir/emtricitabine, tenofovir/lamivudine, and abacavir/lamivudine (essentially excluding backbones containing zidovudine). When restricting to these NRTI backbones, the HIV dementia hazard ratio was attenuated for atazanavir but not for lopinavir, and the hazard ratios for the combined end point were largely unchanged.

When we restricted the analysis to the 29,180 (64%) individuals who initiated cART in 2008 or later, the hazard ratios were attenuated for HIV dementia but not for the combined end point (Fig. 2). When we restricted the analysis to individuals who were aged 50 years or younger at baseline, the HIV dementia hazard ratios comparing atazanavir and lopinavir with efavirenz were larger than in the primary analysis, but the estimates for the combined end point were attenuated (Fig. 2). The confidence intervals in these sensitivity analyses were wide, and there were too few events to look at each opportunistic infection separately. Our results were similar when we used continuous as opposed to categorical baseline variables. None of the other sensitivity analyses described previously yielded appreciably different results.

In the analysis excluding efavirenz regimens, the HIV dementia hazard ratios (95% CIs) were 1.18 (0.64 to 2.19) for lopinavir and 0.96 (0.39 to 2.37) for darunavir, compared with atazanavir. The hazard ratios (95% CIs) for the combined end point were 1.52 (0.93 to 2.50) for lopinavir and 1.12 (0.55 to 2.31) for darunavir, compared with atazanavir (Fig. 2).

DISCUSSION

Our study is the first to examine the potential differences by cART regimen on the risk of clinical diagnoses of neuroAIDS. Our findings are consistent with an increased risk of HIV dementia after initiating cART regimens containing lopinavir or atazanavir and with an increased risk of neuroAIDS opportunistic infections after initiating cART regimens containing lopinavir, compared with efavirenz. However, our findings need to be interpreted with caution because a large proportion of the cases were diagnosed within a few months of initiation, and the increased relative risk was substantially attenuated among individuals initiating cART in 2008 or

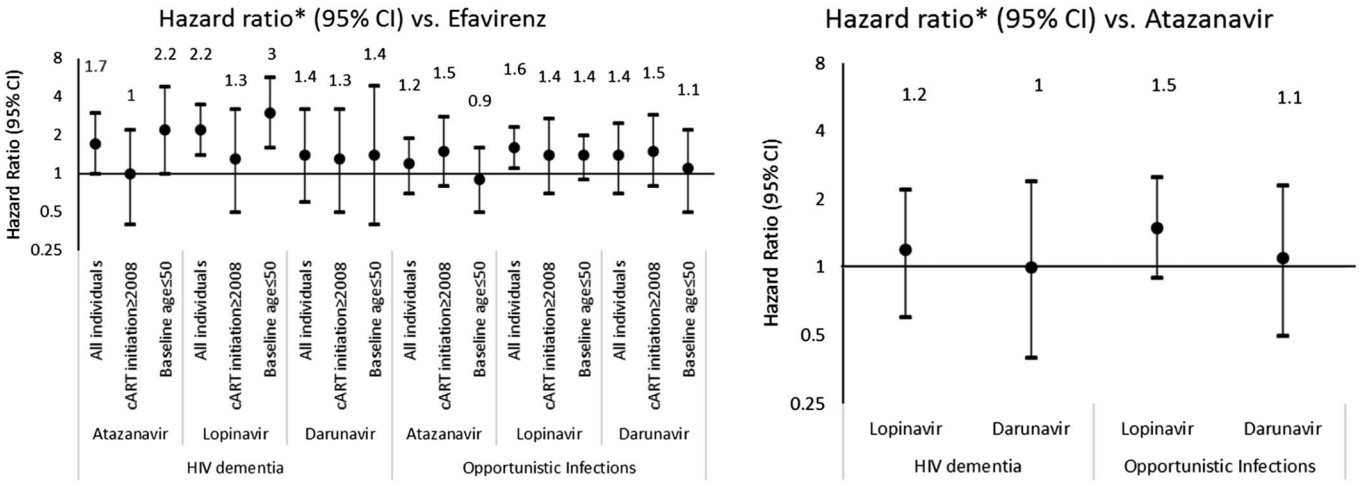

FIGURE 2. NeuroAIDS outcomes by subgroup (left) and excluding efavirenz (right), HIV-CAUSAL Collaboration 2004–2015. *Adjusted for the baseline covariates (sex, age, race, geographic origin, mode of transmission, CD4 cell count, HIV RNA, calendar year, and years since HIV diagnosis). cART initiation ≥2008, analysis restricted to individuals initiating cART in 2008 or later. Baseline age ≤50 years, analysis restricted to individuals less than 50 years at baseline. Full results in Supplemental Digital Content Table 2, http://links.lww.com/QAI/B87 and Supplemental Digital Content Table 3, http://links.lww.com/QAI/B87.

later. It is therefore possible that the increased risk found in our main analysis could be the result of changes in prescribing trends over time such as prescribing zidovudine as an NRTI backbone, prescribing InSTI-based regimens to individuals who could be at higher risk for neuroAIDS, or starting cART at higher CD4 levels.

To the extent that our estimates were causal, possible mechanisms through which cART regimens could affect the incidence of neuroAIDS include penetration of antiretrovirals into the CNS, level of HIV-RNA suppression, and immunologic recovery. cART regimens with greater penetration into the CNS could decrease the risk of HIV dementia by more effectively targeting HIV replication in the brain, but they could also increase HIV dementia risk via deposition of beta-amyloid plaques into the brain.[7,18] However, because lopinavir and efavirenz have the same CNS-penetration effectiveness rankings,[12] CNS penetration may not explain our findings. An effect of cART regimens on HIV dementia could also be explained by differences in HIV-RNA replication or lipid profile[19] after cART initiation. On the other hand, any effect of cART regimens on opportunistic infections is more likely explained by differences in CD4 cell count recovery after cART initiation.[5,20] Randomized trials comparing lopinavir with efavirenz have found no difference in CD4 cell count recovery 48 weeks after cART initiation,[21] a smaller proportion of individuals achieving virologic suppression at 48 weeks[21] and 96 weeks,[22] and a greater increase in triglyceride levels.[21] In our study, the CD4 cell count at the time of event for the combined end point was similar for lopinavir compared with efavirenz.

A causal interpretation of our findings relies on the untestable assumption that the measured covariates were sufficient to adjust for confounding. Confounding by indication might partly explain our estimates if efavirenz was prescribed less frequently to individuals at a higher risk for neuroAIDS. Efavirenz is often avoided in individuals with a history of mental health problems and depression; psychiatric and nervous system symptoms have been reported more frequently in individuals treated with efavirenz, although efavirenz is not contraindicated for individuals at higher risk for neurological conditions.[23] Individuals who initiated lopinavir in our study differed from individuals who initiated other regimens with respect to calendar year and key clinical and demographic factors, suggesting that they could also differ with respect to unmeasured lifestyle, social, and behavioral factors for which we were not able to adjust such as depression, education level, and cardiovascular disease. In general, the unadjusted estimates from our analysis were larger than the adjusted estimates; however, the direction of any remaining unmeasured confounding is unknown.

Our results could also be biased if there are diagnostic delays for the outcomes of interest that are differential with respect to cART regimen. Although we did not have information on the frequency of neurological screening in our study, we found no differences by cART regimen for frequency of CD4 and HIV-RNA monitoring, which may serve as a proxy for frequency of encounters with a medical provider.

Our findings are consistent with an increased risk of neuroAIDS after initiating cART regimens with lopinavir compared with efavirenz, but a causal interpretation is not warranted. The increased risk was diminished in more recent years, perhaps because of individuals initiating cART at higher CD4 cell counts or other changes in prescribing patterns, and confounding by indication is a more likely explanation for our findings. Given the direction of our estimates, our study provides moderate evidence against a negative effect of efavirenz regimens compared with other cART regimens commonly prescribed in the same era on neuroAIDS. Efavirenz is a drug that remains commonly prescribed but for which neurological effects have been a concern. Our study may be useful in informing the design of randomized clinical trials to evaluate the comparative effectiveness of cART regimens on neurologic outcomes.

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