Research Paper

Predictors of Ischemic and Hemorrhagic Strokes Among People Living With HIV: The D:A:D International Prospective Multicohort Study☆

Camilla Ingrid Hatleberg [a,*], Lene Ryom [a], David Kamara [b], Stephane De Wit [c], Matthew Law [d], Andrew Phillips [b], Peter Reiss [e,f], Antonella D'Arminio Monforte [g], Amanda Mocroft [b], Christian Pradier [h], Ole Kirk [a], Helen Kovari [i], Fabrice Bonnet [j], Wafaa El-Sadr [k], Jens D. Lundgren [a], Caroline Sabin [b], for the D:A:D Study Group [1]

[a] Centre of Excellence for Health, Immunity and Infections (CHIP), Department of Infectious Diseases, Section 2100, Rigshospitalet, University of Copenhagen, Denmark
[b] Institute for Global Health, UCL, London, United Kingdom
[c] Division of Infectious Diseases, Saint Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium
[d] The Kirby Institute, UNSW Australia, Sydney, Australia
[e] Amsterdam University Medical Center (location AMC), Dept. of Global Health and Div. of Infectious Diseases, University of Amsterdam, Amsterdam, the Netherlands
[f] HIV Monitoring Foundation, Amsterdam, the Netherlands
[g] Dipartimento di Scienze della Salute, Clinica di Malattie Infettive e Tropicali, Azienda Ospedaliera-Polo Universitario San Paolo, Milan, Italy
[h] Department of Public Health, Nice University Hospital, Nice, France
[i] Division of Infectious Diseases and Hospital Epidemiology, University Hospital of Zurich, University of Zurich, Switzerland
[j] Université de Bordeaux, ISPED, INSERM U1219, CHU de Bordeaux, Bordeaux, France
[k] ICAP-Columbia University, Harlem Hospital, New York, USA

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Data statement:
The D:A:D Study Steering Committee encourages the submission of concepts for research projects. Concepts can be submitted for review by the D:A:D Steering Committee using an online research concept, please see http://www.cphiv.dk/OngoingStudies/DAD/Submit-research-concept. Once submitted the research concept will undergo review by the D:A:D SC for evaluation of the scientific relevance, relevance to the D:A:D Study, design, statistical power and feasibility and overlap with already approved projects. Upon completion of the review, feedback will be provided to the proposer (s). In some circumstances, a revision of the concept may be requested. If the concept is

ABSTRACT

Background: Hypertension is a stronger predictor of hemorrhagic than ischemic strokes in the general population. We aimed to identify whether hypertension or other risk factors, including HIV-related factors, differ in their associations with stroke subtypes in people living with HIV (PLWHIV).

Methods: HIV-1-positive individuals from the Data collection on Adverse events of anti-HIV Drugs (D:A:D) study were followed from the time of first blood pressure (BP) measurement after 1/1/1999 or study entry until the first of a validated stroke, 6 months after last follow-up or 1/2/2014. Stroke events were centrally validated using standardized criteria. Hypertension was defined as one systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg. Poisson and Cox proportional hazards regression models determined associations of established cerebro/cardiovascular disease and HIV-related risk factors with stroke and tested whether these differed by stroke subtype.

Findings: 590 strokes (83 hemorrhagic, 296 ischemic, 211 unknown) occurred over 339,979 person-years (PYRS) (incidence rate/1000 PYRS 1.74 [95% confidence interval (CI) 1.60–1.88]). Common predictors of both hemorrhagic and ischemic strokes were hypertension (relative hazard 3.55 [95% CI 2.29–5.50] and 2.24 [1.77–2.84] respectively) and older age (1.28 [1.17–1.39] and 1.19 [1.12–1.25]). Male gender (1.62 [1.14–2.31] and 0.60 [0.35–0.91]), previous cardiovascular events (4.03 [2.91–5.57] and 1.44 [0.66–3.16]) and smoking (1.90 [1.41–2.56] and 1.08 [0.68–1.71]) were stronger predictors of ischemic then hemorrhagic strokes, whereas hypertension, hepatitis C (1.32 [0.72–2.40] and 0.46 [0.30–0.70]) and estimated glomerular filtration rate <60 mL/min/1.72 m^3 (4.80 [2.47–9.36] and 1.04 [0.67–1.60]) were stronger predictors of hemorrhagic than ischemic strokes. A CD4 count < 200 cells/μL was associated with an increased risk of hemorrhagic stroke only.

Interpretation: Risk factors for stroke may differ by subtype in PLWHIV, emphasizing the importance of further research to increase the precision of stroke risk estimation.

Research in context

Evidence before this study

Pubmed search: We used PubMed to identify previous studies on stroke and stroke risk factors in people living with HIV, using search terms "stroke and HIV", "cardiovascular disease and HIV", "cerebrovascular disease and HIV", "ischemic strokes and HIV", and "hemorrhagic strokes and HIV". The search included studies up to June 10, 2018, with no language restrictions. To date, most studies on stroke in this population consider ischemic strokes only or a composite endpoint that includes both ischemic and hemorrhagic strokes and/or other forms of cerebro/cardiovascular disease. The etiology of increased stroke risk in people living with HIV includes a higher prevalence of traditional cerebro/cardiovascular disease risk factors and factors relating to immunosuppression and inflammation such as HIV-vasculopathy and immune reconstitution. Multiple risk factors have been associated with an increased risk of stroke, including age, hypertension, diabetes, dyslipidemia, smoking, hepatitis C virus, and injection drug use. Findings are conflicting, however, on the importance of immunosuppression and viral replication for stroke risk. In the general population it is known that ischemic and hemorrhagic strokes have distinct risk profiles, and although the two types of strokes share several common risk factors, hypertension and low estimated glomerular rate have been shown to be more strongly linked to hemorrhagic than ischemic strokes, whereas ischemic stroke is more strongly linked to metabolic risk factors. As no previous studies on stroke risk in people living with HIV have formally compared risk profiles for the two stroke types, it is unknown whether hypertension, other traditional cerebro/cardiovascular disease risk factors and/or HIV-related factors differ significantly in their impact on risk for ischemic versus hemorrhagic stroke.

Added value of this study

Five-hundred and ninety centrally validated strokes occurred over 339,979 person-years of follow-up from 1999 to 2014. In formal comparison models (83 hemorrhagic and 296 ischemic strokes), we found the strongest common predictors to be hypertension and older age. Male gender, previous cardiovascular events, and smoking were stronger predictors of ischemic strokes, whereas hypertension, hepatitis C virus coinfection and estimated glomerular filtration rate <60 mL/min/1.72 m^3 were stronger predictors of hemorrhagic strokes. A CD4 count <200 cells/μL was associated with a borderline increased risk of hemorrhagic but not ischemic stroke, whereas a higher viral load and exposure to antiretroviral therapy were not associated with the risk of either stroke subtype. Although we were limited by a relatively low number of hemorrhagic strokes, findings from this large, heterogeneous cohort with centrally validated separate stroke endpoints suggest that some traditional and HIV-related risk factors may differ by stroke subtype in people living with HIV.

Implications of all available evidence

With the well-documented increased risk of stroke in the HIV-positive population, screening and preventive treatments are becoming increasingly important as this population is aging. As the risk of complications (e.g. bleeding) of anti-thrombotic therapy increases with age, stroke risk stratification which takes into account traditional cerebro/cardiovascular risk factors as well as HIV-related factors, may help to determine the relative benefits and risks of such therapy. Our findings indicate that the use of stratified predictors may provide more precise risk estimates. Further studies are needed to confirm our findings, in order to individualize and optimize stroke prevention and management leading to improved outcomes.

1. Introduction

Stroke is a major cause of mortality, morbidity and disability worldwide. Ischemic stroke is the most common stroke subtype, accounting for nearly 90% of all strokes, whereas hemorrhagic strokes have a higher fatality rate [1]. In people living with HIV (PLWHIV), an increased risk of cerebro/cardiovascular disease (CVD) is well documented across diverse clinical settings and populations [2–6]. Multiple factors are likely to contribute to this increased risk, including a higher prevalence of common CVD risk factors such as hypertension, diabetes, dyslipidemia, renal impairment and smoking [2,5–8], the pro-atherogenic effects of certain antiretroviral (ARV) drugs [4,6,9,10] and HIV-related inflammation, immune activation and microbial translocation [11]. In addition, hypercoagulability and inflammation-induced intracranial vasculopathy may also play a role [6,12,13].

Although cerebrovascular and cardiovascular diseases exhibit similarities in risk factors and pathophysiology, cerebrovascular disease is generally more heterogeneous, and ischemic and hemorrhagic strokes have distinct risk profiles. In PLWHIV, the heterogeneous nature of stroke pathophysiology and clinical presentations, which may be complicated by neuro-infections mimicking stroke, means that few studies have considered stroke outcomes; studies of hemorrhagic stroke as a separate endpoint are limited [3,6,14] and thus, to date, most studies in this population have considered ischemic strokes or a composite endpoint of both stroke subtypes and/or other forms of CVD [2,4,6,8]. In the general population, several shared risk factors for ischemic and hemorrhagic strokes have been identified including hypertension, renal impairment, age, ethnicity, diabetes, obesity and smoking [15]. Hypertension and low estimated glomerular rate (eGFR) are more strongly linked to hemorrhagic than ischemic strokes [16,17], whereas

ischemic stroke is typically more strongly linked to metabolic risk factors [15].

As in the general population, risk factor stratification may be of value in PLWHIV; risk factors may vary or have opposing effects on the two stroke subtypes, and preventive medications, such as anti-thrombotic therapy, have opposing effects on risk of ischemic and hemorrhagic strokes [18]. The effects of some common CVD risk factors may, however, differ in PLWHIV, and we do not know whether HIV-related factors are also differentially associated with ischemic and hemorrhagic strokes. As the HIV-positive population ages, and the risk of complications of anti-thrombotic therapy, such as bleeding, increases, stroke risk stratification which takes into account both common CVD risk factors and HIV-related factors, could be helpful when determining the relative benefits and risks of such therapy.

By identifying their respective risk for each stroke subtype, it may be possible to influence clinical decision-making, individualize and optimize stroke prevention and management and improve outcomes. Our aim was to investigate systematically whether hypertension, other common CVD risk factors and HIV-related factors were differently associated with ischemic and hemorrhagic strokes in the D:A:D (Data Collection on Adverse events of anti-HIV Drugs) Study.

2. Material and Methods

2.1. Study Design, Study Participants and Outcomes

The D:A:D Study is a large, prospective observational cohort study which followed >49,000 HIV-1-positive persons from 11 collaborating cohorts receiving care at 212 hospital clinics in Australia, Europe and USA, who together contributed >450,000 person-years (PYRS) of follow-up (for participating institutions, see Appendix). The primary aim of the study, described previously [19], was to investigate associations between the use of ARV drugs and risk of CVD. The data collected included information on socio-demographic factors, HIV-related and other laboratory markers, ARV regimen/history and CVD risk factors/ treatments. Data were reported to the D:A:D coordinating center as anonymous, computerized case report files which were then merged into a standardized central dataset. All cases of stroke were validated centrally by a trained medical doctor, against a validated stroke algorithm (https://www.chip.dk/Portals/0/files/Study%20documents/DAD_MOOP_revised2013.pdf) based on the presence of focal neurological signs (with/without additional imaging), with duration >24 h and no evidence of any non-vascular cause. Accepted stroke events were classified as definite or possible depending on the level of certainty. The differentiation of strokes into the ischemic and hemorrhagic subtypes was undertaken based on imaging data; where imaging data were unavailable, strokes were classified as being of unknown etiology.

This analysis was conducted in accordance with the Declaration of Helsinki, with approval by national ethics committees and informed consent where required by national regulations. All participating cohorts followed local national guidelines/regulations regarding patient consent and/or ethical review. In particular, of the countries represented, only Switzerland and Australia required specific ethical approval for D:A:D in addition to that required for their national cohorts (Swiss HIV Cohort Study and AHOD), both of which have obtained this approval. France, Italy, and Belgium do not require specific ethical approval over-and-above that required for the individual cohorts (Nice/ Aquitaine, Brussels St. Pierre and IcoNA, respectively). Neither the Netherlands (ATHENA) nor the United States (CPCRA) requires specific ethical approval as data are provided as part of HIV care and as the datasets are non-identifiable public use datasets. For the EuroSIDA study (including data from the BASS and Swedish cohorts), which includes participants from many European countries, each participating site has a contractual obligation to ensure that data collection and sharing is done in accordance with national legislation; each site principal investigator either maintains appropriate documentation from an ethical committee (if required by law) or has a documented written statement to say that this is not required.

2.2. Statistical Methods

We followed D:A:D Study participants from the time of the first blood pressure (BP) measurement from 1/1/1999 or individual study entry until the first of a validated stroke, 6 months after last follow-up or 1/2/2014. We calculated incidence rates (IRs) separately for ischemic, hemorrhagic and unknown stroke subtypes, overall and after stratification by the presence or absence of hypertension over follow-up, which we defined as a single systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg (regardless of the use of anti-hypertensive medication). If BP values subsequently changed, we also allowed the hypertensive status of an individual to change in a time-updated manner.

After censoring the follow-up of individuals with an unknown stroke subtype (where radiological information was missing or subtype uncertainty remained) at the time of the event, we initially explored whether the associations of several factors with stroke risk differed by stroke subtype, fitting a multivariable Poisson regression model to ischemic and hemorrhagic strokes separately. We considered the following risk factors: socio-demographic (gender, ethnicity (both time-fixed covariates), age (/5 years older), calendar year), CVD-related (dyslipidemia (defined as total cholesterol ≥ 6.2 mmol/L, HDL ≤ 0.9 mmol/L, or triglyceride ≥ 2.3 mmol/L), previous CVD event (myocardial infarction (MI)/stroke), family history of CVD, body mass index (BMI), diabetes, smoking status (all time-updated)) and HIV-related (mode of HIV-acquisition (time-fixed), previous AIDS diagnosis, latest HIV-RNA viral load (VL) and CD4 count, cumulative exposure (/5 years) to protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs)), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection (all time-updated).

As these exploratory analyses did not control for competing risks, we then formally compared the reported associations with each stroke subtype using modified Cox proportional hazards models which took account of competing risks. This allowed us to investigate whether risk factors appeared to differ by stroke subtype. We compared the predictive value of each selected risk factor for the two stroke subtypes in a model that included adjustment for all other potential confounders, but in which only the selected risk factor was allowed to have different associations with the two subtypes. These models therefore allowed us to estimate the common association of each factor with the two stroke subtypes and to test whether this association differed significantly by stroke subtype. Note that in order to reduce the number of statistical tests performed, we only investigated interactions for factors that would be of direct clinical relevance (for example, interactions with 'unknown smoking status' were not considered) or where our exploratory analyses had suggested either a qualitatively different association or a substantial quantitative difference in association. Thus, for mode of HIV acquisition, we only allowed the association with IDU status to vary, for BMI we only allowed the lowest category (<18 kg/m^2) to vary and for smoking status, only current smoking was allowed to vary. As some of these factors were themselves correlated (e.g. HCV and IDU mode of HIV acquisition), we then fitted models that allowed multiple risk factors to simultaneously have subtype-specific effects, removing factors and interactions that no longer demonstrated a strong association with the outcome.

In a sub-analysis, we additionally included Cockcroft-Gault estimated eGFR as an additional time-updated covariate (2 consecutive measurements, 3 months apart) after restricting follow-up to the start of systematic collection of eGFR in the study (1/2/2004). Since general population studies have normally used a definition of hypertension that requires two consecutive elevated BP measurements [17], we also investigated the robustness of our findings to changes in the definition of hypertension, requiring individuals to have two consecutive elevated BP measurements to meet the criteria.

Statistical analyses were performed using SAS v9.3.

2.3. Role of the Funding Source

The funders had no direct role in study design, data collection, analysis, interpretation, report writing, or the decision to submit for publication. The corresponding author had full access to all data and had responsibility for submission for publication.

3. Results

3.1. Characteristics of Study Participants

Of the total 43,564 individuals included, the majority of participants with stroke were male, white, had acquired HIV through sex between men, were current smokers and had been exposed to ARV drugs at the time of their stroke event, whereas just under half had hypertension. Characteristics of participants at the time of their stroke, overall and stratified by stroke subtype, are displayed in Table 1.

3.2. Incidence of Stroke Subtypes and Association With Hypertension

Over the follow-up period of 339,979 PYRS, there were 590 strokes (IR: 1.74, 95% confidence interval [CI] [1.60, 1.88]/1000 PYRS). Nearly half of the strokes were ischemic, whereas around two-thirds and one-third, respectively, were of unknown and hemorrhagic origin (Table 2). The crude IRs for stroke, overall and for each sub-type, were higher in those with hypertension than in those without (Table 2).

3.3. Exploratory Analysis of Stroke Risk Factors for Ischemic and Hemorrhagic Stroke

Poisson regression models suggested that the risk factor profile for the two main stroke subtypes differed (Fig. 1). Ischemic strokes appeared to be more strongly associated with traditional CVD risk factors

(male gender, dyslipidemia, previous CVD, diabetes, smoking) and previous AIDS than were hemorrhagic strokes. Conversely, while hypertension was associated with both stroke subtypes, its association appeared to be stronger for hemorrhagic strokes than for ischemic strokes (adjusted relative rate 3.53 [2.23–5.58] for ischemic and 2.10 [1.65–2.65] for hemorrhagic) (Fig. 1a), a similar pattern to that seen for a CD4 count <200 cells/μL. While HCV and HBV both appeared to be associated (non-significantly so) with an increased risk of hemorrhagic stroke, their associations with ischemic stroke appeared to be in the opposite direction (Fig. 1b).

3.4. Formal Comparison of Risk Factors for Hemorrhagic and Ischemic Strokes

In line with our exploratory analyses, hypertension appeared to be a stronger risk factor for hemorrhagic than ischemic strokes, although the association was of only borderline significance (Table 3). Other risk factors that appeared to differ significantly in their predictive ability for either stroke subtype were male gender, current smoking and a previous CVD event, each of which appeared to be stronger predictors of ischemic than hemorrhagic strokes (Table 3). Conversely, IDU mode of HIV infection and anti-HCV positivity/HCV infection were significantly stronger predictors for hemorrhagic than for ischemic strokes. Of the HIV-related factors, a current CD4 count <200 cells/μL was a stronger risk factor for hemorrhagic strokes than for ischemic strokes although the difference in predictive ability was only borderline significant (Table 3).

In a further model which allowed more than one risk factor to interact with the stroke outcomes simultaneously (Table 4), the association for hypertension was strengthened and was a significantly stronger predictor for hemorrhagic than ischemic strokes. It also became clear that the difference seen in the association with IDU status was largely explained by a higher rate of anti-HCV positivity in those infected through IDU. In this full multivariable model, therefore, the difference in

Table 1
Characteristics of all study participants at baseline and at time of stroke, overall and stratified by stroke type.

		At study entry	At time of stroke			
			Total	Hemorrhagic	Ischemic	Unknown
		N (%)	N (%)	N (%)	N (%)	N (%)
Total number of participants		43,564	590	83	296	211
Demographic/CVD-related						
Gender	Male	32,064 (73.6)	481 (81.5)	56 (67.5)	251 (84.8)	174 (82.5)
Age (years)	Median (IQR)	39 (33–46)	55 (46–64)	52 (46–59)	55 (46–63)	54 (46–63)
Ethnicity	White	22,418 (51.5)	310 (52.5)	37 (44.6)	142 (48.0)	131 (62.1)
Smoking status	Current smoker	18,250 (41.9)	262 (44.4)	34 (41.0)	145 (49.0)	83 (39.3)
	Ex-smoker	7648 (17.6)	140 (23.7)	22 (26.5)	64 (21.6)	54 (25.6)
	Never/unknown	17,666 (40.6)	188 (31.9)	27 (32.5)	87 (29.4)	74 (35.1)
Previous CVD event	Yes	662 (1.5)	108 (18.3)	7 (8.4)	55 (18.6)	46 (21.8)
Family history of CVD	Yes	3100 (7.1)	67 (11.4)	9 (10.8)	37 (12.5)	21 (10.0)
Hypertension	Yes	10,281 (23.6)	293 (49.7)	49 (59.0)	150 (50.7)	94 (44.6)
Diabetes	Yes	1340 (3.1)	95 (16.1)	9 (10.8)	54 (18.2)	32 (15.2)
Dyslipidemia	Yes	17,490 (40.2)	351 (59.5)	44 (53.0)	181 (61.2)	126 (59.7)
BMI (kg/m^2)	Median (IQR)	23 (21–25)	23 (21–26)	23 (21–27)	23 (21–26)	23 (21–26)
eGFR (mL/min/L.72 m^3)	Median (IQR)	104 (89–121)	84 (67–99)	80 (62–98)	83 (67–100)	85 (71–100)
HIV-related						
Previous AIDS event	Yes	10,019 (23.0)	237 (40.2)	33 (39.8)	126 (42.6)	78 (37.0)
Ever received ART	Yes	30,089 (69.1)	565 (95.8)	79 (95.2)	288 (97.3)	198 (93.8)
Mode of HIV-acquisition	MSM[a]	19,183 (44.0)	266 (45.1)	30 (36.1)	135 (45.6)	101 (47.9)
	IDU	6580 (15.1)	82 (13.9)	17 (20.5)	35 (11.8)	30 (14.2)
	Heterosexual	15,126 (34.7)	192 (32.5)	29 (34.9)	97 (32.8)	66 (31.3)
	Other/unknown	2675 (6.1)	50 (80.5)	7 (8.4)	29 (9.8)	14 (6.6)
CD4 (cells/μL)	Median (IQR)	423 (270–610)	446 (250–650)	455 (262–760)	461 (270–688)	390 (213–600)
HIV RNA (log$_{10}$ copies/mL)	Median (IQR)	2.5 (1.7–4.2)	1.7 (1.7–2.5)	1.7 (1.7–2.1)	1.7 (1.7–2.2)	1.7 (1.7–3.0)
HCV positive[b]	Positive	7686 (17.6)	113 (19.2)	26 (31.3)	44 (14.9)	43 (20.4)
HBV positive[c]	Positive-active	1962 (4.5)	15 (2.5)	4 (4.8)	9 (3.0)	2 (1.0)

IDU: injection drug use; MSM: men who have sex with men; BMI: body mass index; eGFR: estimated glomerular filtration rate; PI: protease inhibitor; NNRTI: non-nucleoside transcriptase inhibitor; NRTI: nucleoside transcriptase inhibitor.

[a] MSM: men who have sex with men.
[b] HCV-antibody positive and/or HCV-RNA positive.
[c] HB surface antigen, HBe antigen or HBV DNA + positive.

Table 2
Incidence of any stroke and each stroke subtype (/1000 PYRS) overall and stratified by the presence or absence of hypertension.

Type of stroke[a]	Overall		No hypertension		Hypertension	
	N stroke events/PYRS	Rate/1000 PYRS (95% CI)	N stroke events/PYRS	Rate/1000 PYRS (95% CI)	N stroke events/PYRS	Rate/1000 PYRS (95% CI)
All	590/339,979	1.74 (1.60, 1.88)	297/255133	1.16 (1.03, 1.30)	293/84,850	3.45 (3.06, 3.85)
Hemorrhagic	83/341,962	0.24 (0.19, 0.30)	34/256,307	0.13 (0.09, 0.18)	49/85,660	0.57 (0.41, 0.73)
Ischemic	296/340,995	0.87 (0.77, 0.97)	148/255,698	0.58 (0.49, 0.67)	148/85,297	1.74 (1.46, 2.02)
Unknown	211/341,357	0.62 (0.54, 0.70)	115/255,939	0.45 (0.37, 0.53)	96/85,424	1.12 (0.90, 1.35)

[a] Stroke event censored after first hemorrhagic/ischemic stroke event.

association with IDU between the two stroke subtypes was reduced substantially and was no longer significant.

3.5. Sensitivity Analyses

An eGFR < 60 mL/min/1.72 m^3 appeared to be more strongly associated with hemorrhagic than with ischemic strokes (hemorrhagic stroke 2.85 [1.45–5.64] vs. ischemic stroke 1.00 [0.68–1.48]) in exploratory analyses, a finding which was confirmed in the formal comparison model (4.81 [2.47–9.36] vs. 1.04 [0.67–1.59], $p_{equal} < 0.001$). Our conclusions were not significantly changed when re-defining hypertension on the basis of two consecutive elevated BP measurements (data not shown).

4. Discussion

In this large, observational study of PLWHIV, we observed several differences in the risk factor profiles for ischemic and hemorrhagic strokes. Firstly, while hypertension and age were the strongest common risk factors for both stroke subtypes, ischemic strokes appeared to be more strongly linked to male gender, smoking, previous CVD events and metabolic risk factors whereas hemorrhagic strokes appeared to be more strongly linked to hypertension, a low CD4 count, anti-HCV positivity and, in a smaller sub-analysis, renal impairment. While our study was limited by the number of stroke events, particularly hemorrhagic strokes, we did find a statistically significant difference for hypertension, gender, smoking, previous CVD events, HCV and renal impairment.

Hypertension is recognized as a major risk factor for both types of stroke [15], but has been observed to be a stronger predictor for hemorrhagic than ischemic strokes in the general population [15,17]. We observed a similar difference in the association between hypertension and each stroke-subtype (3-fold higher for hemorrhagic but 2-fold higher for ischemic) as has been reported in the general population; the difference was statistically significant when associations were formally compared.

The aging HIV population represents a new clinical challenge due to a higher prevalence of CVD risk factors, comorbidities and polypharmacy. The risk of stroke steadily increases with age [1]; as in the general population [15], our analyses suggested that the predictive ability of age did not differ greatly by stroke type. While our exploratory analyses suggested that metabolic factors, including diabetes, dyslipidemia and BMI, were more strongly associated with ischemic than hemorrhagic strokes in PLWHIV, largely consistent with findings from the general population [15], differences in predictive ability were not significant when tested formally, possibly reflecting a reduction in power due to the small number of hemorrhagic strokes included.

While male gender was a significantly stronger predictor of ischemic than hemorrhagic strokes in our analyses, as reported in the general population [15], female gender appeared to be a stronger predictor for hemorrhagic stroke. Similar findings in PLWHIV have been reported by Chow et al. [3].

A previous CVD event was a significantly stronger predictor for ischemic strokes, potentially due to fewer prior hemorrhagic events that also have higher fatality rates [1]. Suboptimal medical secondary

prophylaxis has been reported in PLWHIV [20] emphasizing the importance of optimizing CVD risk prevention and treatment.

Current smoking was associated with an almost 2-fold increased risk of ischemic strokes and was a significantly stronger predictor of these than hemorrhagic strokes. Although smoking is an important risk factor for both stroke types in the general population, studies have generally indicated a stronger association with ischemic stroke [15,21]. It is unclear why we do not find an association between current smoking and hemorrhagic stroke in our HIV cohort, although this may be a consequence of reduced power due to the small number of such events.

While IDU was a stronger predictor for hemorrhagic strokes, the association appeared to be primarily driven by concomitant HCV infection, which appeared to be a potential risk factor for hemorrhagic stroke but was strongly associated with a reduced risk of ischemic stroke. In contrast, a similar increased risk has been observed between HCV infection and both hemorrhagic [22] and ischemic strokes [23] in the general population. In PLWHIV, HCV has been reported to be a strong predictor for hemorrhagic strokes [14], as has an increased risk of composite endpoints of cerebro/cardiovascular nature with HIV/HCV co-infection [24], suggesting a persistent inflammatory state where HIV and HCV may act synergistically [24]. For hemorrhagic strokes specifically, the inflammation-induced vasculitis changes in cerebral arteries associated with other viruses (varicella zoster virus, cytomegalovirus and HIV) may trigger bleeding [25], as can the coagulation abnormalities associated with severe HCV-disease manifestations [26]. The lack of an association between HCV and ischemic stroke in our study might reflect a selection of HCV co-infected individuals in our cohort with more severe HCV disease at higher risk of bleeding. More research is needed to further examine the nature of these associations and whether eradication of HCV with direct acting antivirals can revert this risk in PLWHIV. However, our findings along with previous studies argue that HCV-monitoring should be included in CVD risk screening and that HCV-treatment should potentially be considered in all HIV/HCV-infected individuals regardless of HCV disease stage.

In contrast to HCV, no significant association has previously been demonstrated between HBV and increased CVD risk in PLWHIV [6]. In our analysis, a small apparent difference in predictive risk of HBV with the different stroke subtypes was not seen in the model allowing multiple factors to vary simultaneously, which is consistent with previous data [6].

Previous reports on the impact of both CD4 count and HIV VL on ischemic stroke risk or composite stroke endpoints in PLWHIV have been conflicting [2,4,6,8]. In unadjusted analyses, we observed a strong association between low current CD4 count and increased risk of hemorrhagic stroke but not ischemic stroke, although the difference in predictive ability was non-significant and the CD4 count did not meet our threshold for inclusion in the final multivariable model. While we cannot rule out the possibility that an association was missed due to a lack of power, and as such any conclusions must be made with caution, these results are consistent with some previous studies [3,14]. Furthermore, rigorous validation methods in our cohort reduce the risk of including AIDS-related conditions mimicking stroke, arguing that HIV-related intracerebral immune-deficiency may indeed increase the risk of hemorrhagic stroke. Biological mechanisms behind increased hemorrhagic stroke risk with low CD4 count may be explained by two types of
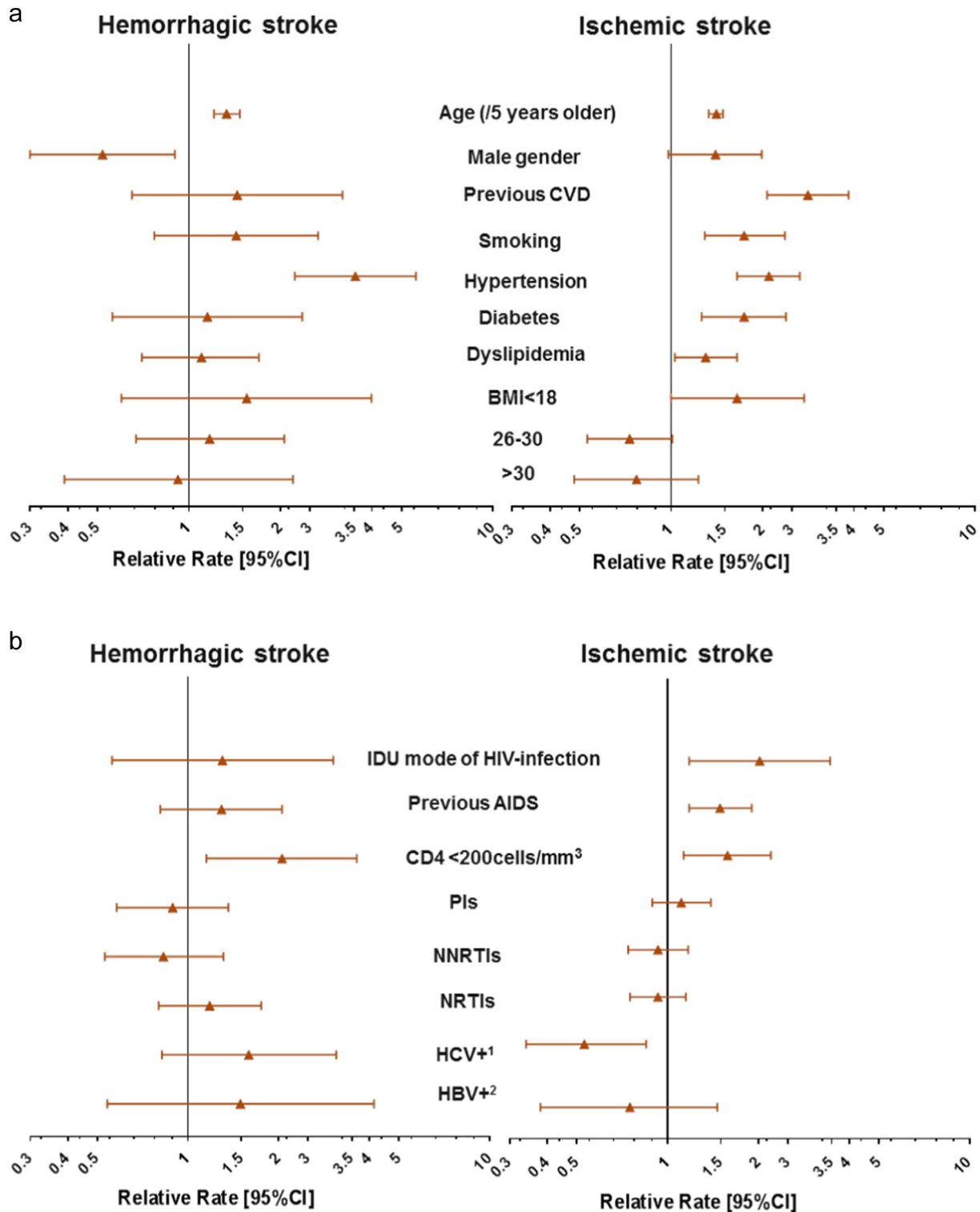
Fig. 1. a: Association between demographic and CVD-related factors, exploratory multivariable Poisson models for 83 hemorrhagic and 296 ischemic strokes. Footnotes: Reference groups: Male gender: Female gender; Previous CVD: No previous CVD; Smoking: never smoked; Hypertension: No hypertension; Diabetes: No diabetes; Dyslipidemia: No dyslipidemia; body mass index (BMI): 18–25. Additionally adjusted for: Age, elevated BP, gender, BMI, smoking, previous CVD, diabetes, dyslipidemia. 1: HCV-antibody pos./HCV-RNA pos. 2: Active [HB surface antigen, HBe antigen or HBV DNA + pos.]. b: Association between HIV-related factors and stroke, exploratory multivariable Poisson models for 83 hemorrhagic and 296 ischemic strokes. Footnotes: Reference groups: Injection drug use (IDU): Men who have sex with men; previous AIDS: No previous AIDS; CD4 count: CD4 count > 200 cells/μL; protease inhibitors (PIs): Never exposed to PIs; non-nucleoside reverse transcriptase inhibitors (NNRTIs): Never exposed to NNRTIs; nucleoside reverse transcriptase inhibitors (NRTIs): Never exposed to NRTIs; hepatitis C (HCV): Never HCV positive; hepatitis B (HBV): Never HBV positive. Additionally adjusted for: Mode of HIV-infection, CD4 count, exposure to ART, previous AIDS.

arterial remodeling; endothelial dysfunction related to immunosuppression and inflammation leading to the destructive process by lipohyalinosis affecting cerebral small vessels [3], and a non-atherosclerotic dolichoectatic arterial phenotype previously associated with prolonged immune impairment in HIV [12,27]. Immune reconstitution may also affect the arterial wall leading to increased risk of stroke

Table 3
Association between each potential risk factor and stroke when each parameter is included in a separate competing risk model.[a]

Risk factor	Event		Hazard ratio	95% confidence interval		Hazard ratio p value	p-Value for overall average effect[b]	p-Value for test of equal effects[c]
Age/5 years		Hemorrhagic	1.28	1.17	1.39	<0.001	<0.001	0.14
		Ischemic	1.19	1.12	1.25	<0.001		
Gender	Male	Hemorrhagic	0.56	0.35	0.91	0.020	<0.001	<0.001
		Ischemic	1.62	1.14	2.31	0.008		
	Female		1.00	–	–	–		
Hypertension	Yes	Hemorrhagic	3.55	2.29	5.50	<0.001	<0.001	0.070
		Ischemic	2.24	1.77	2.84	<0.001		
	No		1.00	–	–	–		
Previous CVD event	Yes	Hemorrhagic	1.44	0.66	3.16	0.34	<0.001	0.016
		Ischemic	4.03	2.91	5.57	<0.001		
	No		1.00	–	–	–		
Dyslipidemia	Yes	Hemorrhagic	0.97	0.63	1.49	0.88	0.006	0.10
		Ischemic	1.48	1.16	1.83	0.001		
	No		1.00	–	–	–		
Diabetes	Yes	Hemorrhagic	1.21	0.57	2.43	0.60	0.008	0.42
		Ischemic	1.65	1.20	2.27	0.002		
	No		1.00	–	–	–		
Mode of HIV infection	IDU	Hemorrhagic	2.68	1.38	5.17	0.004	0.002	0.040
		Ischemic	1.37	0.82	2.29	0.22		
	MSM		1.00	–	–	–		
	Heterosexual		1.27	0.97	1.67	0.083		
	Missing		1.62	1.12	2.33	0.010		
BMI (kg/m^2)	<18	Hemorrhagic	1.79	0.72	4.48	0.21	0.20	0.65
		Ischemic	1.41	0.85	2.34	0.18		
	18, <26		1.00	–	–	–		
	26, <30		0.79	0.58	1.06	0.11		
	≥30		1.09	0.71	1.66	0.69		
	Missing		0.58	0.34	0.97	0.039		
Smoking status	Yes	Hemorrhagic	1.08	0.68	1.71	0.75	<0.001	0.030
		Ischemic	1.90	1.41	2.56	<0.001		
	Ex-smoker		1.04	0.76	1.43	0.82		
	Never		1.00	–	–	–		
	Missing		1.47	1.00	2.17	0.048		
HIV RNA (copies/mL)	>500	Hemorrhagic	1.03	0.58	1.82	0.92	0.22	0.34
		Ischemic	1.36	0.96	1.94	0.083		
	≤500		1.00	–	–	–		
CD4 count (cells/μL)	<200	Hemorrhagic	1.94	1.09	3.45	0.025	0.082	0.065
		Ischemic	1.03	0.69	1.53	0.89		
	≥200		1.00	–	–	–		
PI exposure/5 years		Hemorrhagic	1.10	0.70	1.74	0.66	0.90	0.70
		Ischemic	0.98	0.74	1.31	0.91		
NNRTI exposure/5 years		Hemorrhagic	0.80	0.51	1.27	0.35	0.12	0.76
		Ischemic	0.74	0.55	0.10	0.050		
NRTI exposure/5 years		Hemorrhagic	1.25	0.62	2.51	0.54	0.12	0.72
		Ischemic	1.44	1.00	2.08	0.048		
Previous AIDS event	Yes	Hemorrhagic	1.33	0.85	2.09	0.22	0.013	0.89
		Ischemic	1.38	1.09	1.74	0.007		
	No		1.00	–	–	–		
HCV positive[d]	No		1.00	–	–	–		
	Yes	Hemorrhagic	1.32	0.72	2.40	0.37	<0.001	<0.001
		Ischemic	0.46	0.23	0.70	<0.001		
	Unknown		1.57	0.70	2.48	0.052		
HBV positive[e]	No		1.00	–	–	–		
	Yes (active)	Hemorrhagic	1.19	1.12	1.25	<0.001	0.76	0.076
		Ischemic	1.22	0.90	1.65	0.12		
	Yes (inactive)	Hemorrhagic	2.47	2.01	3.04	<0.001	0.46	0.35
		Ischemic	3.35	2.48	4.54	<0.001		
	Unknown		1.33	1.09	1.63	0.006		

CVD: cardiovascular disease; IDU: injection drug use; MSM: men who have sex with men; BMI: body mass index; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; HCV: hepatitis C virus; HBV: hepatitis B virus.

[a] The parameter estimates displayed in the table arise from a series of separate competing risk Cox proportional hazard models in which the association with the indicated parameter is allowed to vary by stroke subtype (all other factors in the model are assumed to have the same association with each stroke subtype).

[b] The p-value for the overall average effect tests the null hypothesis that there is no overall association between the parameter and stroke.

[c] The p-value for equal effects tests the null hypothesis that the association between the parameter and stroke is the same for the two stroke subtypes (with rejection of the null hypothesis if p < 0.05, suggesting that any difference in the predictive value for the two stroke subtypes was unlikely to be a chance finding).

[d] HCV-antibody positive and/or HCV-RNA positive.

[e] HB surface antigen, HBe antigen or HBV DNA + positive.

after start of ARVs [13,28], which may argue for increased attention to stroke prevention in PLWHIV with low CD4 nadir and subsequent immune reconstitution. Conversely, we did not observe a significantly increased risk of either stroke type with a detectable VL (>500 copies/mL).

Increased stroke risk has previously been associated with abacavir use [4,6] and cumulative PI exposure [9]. In our study, including a larger number of stroke events and adjustment for potential confounders, no association was observed between cumulative exposure to ARVs and

Table 4
Association between each risk factor and stroke when parameters are fitted in a single competing risks model.[a]

Risk factor	Category	Stroke subtype	Hazard ratio	95% confidence interval		p value	p-Value for overall average effect[b]	p-Value for test of equal effects[c]
Age/5 years			1.20	1.14	1.26	<0.001		
Gender	Male	Hemorrhagic	0.62	0.39	1.01	0.054	0.004	0.001
		Ischemic	1.59	1.11	2.27	0.011		
	Female		1.00	–	–	–		
Hypertension	Yes	Hemorrhagic	3.96	2.560	6.11	<0.001	<0.001	0.021
		Ischemic	2.22	1.78	2.81	<0.001		
	No		1.00	–	–	–		
Previous CVD event	Yes	Hemorrhagic	1.61	0.73	3.56	0.24	<0.001	0.039
		Ischemic	3.91	2.83	5.41	<0.001		
	No	1.00	–	–	–	–		
Mode of HIV infection	MSM		1.00	–	–	–		
	IDU	Hemorrhagic	1.58	0.60	4.17	0.36	0.079	0.89
		Ischemic	1.75	1.04	2.95	0.035		
	Heterosexual		1.34	1.03	1.76	0.032		
	Missing		1.89	1.30	2.69	0.001		
Smoking status	Current	Hemorrhagic	0.96	0.59	1.61	0.92	<0.001	0.013
		Ischemic	1.93	1.43	2.5	<0.001		
	Ex-smoker		0.78	0.57	1.05	0.10		
	Never		1.00	–	–	–		
	Unknown		1.43	0.93	2.20	0.10		
HCV positive[d]	No		1.00	–	–	–		
	Yes	Hemorrhagic	1.54	0.70	3.40	0.28	<0.001	0.006
		Ischemic	0.43	0.27	0.68	0.000		
	Unknown	Hemorrhagic	1.60	0.79	3.22	0.19	0.14	0.97
		Ischemic	1.57	0.92	2.69	0.10		

CVD: cardiovascular disease; IDU: injection drug use; MSM: men who have sex with men; HCV: hepatitis C virus; HBV: hepatitis B virus.

[a] The parameter estimates displayed in the table arise from a single Cox proportional hazard model in which all associations with the indicated parameters are allowed to vary by stroke subtype simultaneously.

[b] The p-value for the overall average effect tests the null hypothesis that there is no overall association between the parameter and stroke.

[c] The p-value for equal effects tests the null hypothesis that the association between the parameter and stroke is the same for the two stroke subtypes (with rejection of the null hypothesis if p < 0.05, suggesting that any difference in the predictive value for the two stroke subtypes was unlikely to be a chance finding).

[d] HCV-antibody positive and/or HCV-RNA positive.

increased risk of any of the two stroke subtypes. Although clinicians may have moved away from older ARVs known to be associated with increased CVD risk, our findings are supported by several other previous studies [2,3,6,8,29], and the overall evidence for ARV exposure as a significant stroke risk factor seems scarce.

We found low eGFR to be a significantly stronger predictor for hemorrhagic than ischemic strokes, with similar risk estimates previously reported in the general population [16]. Adjustment for other CVD risk factors did not markedly affect the eGFR estimate, possibly implying a causal relationship between low eGFR and hemorrhagic stroke; low eGFR may induce platelet dysfunction leading to prolonged bleeding time and increasing risk of cerebral hemorrhages [16], or be correlated with cerebral small vessel disease, the mechanism behind most brain hemorrhages [16,30]. We have previously demonstrated associations between lower eGFRs and composite endpoints of CVD [7] and current findings emphasize the importance of renal monitoring in overall CVD risk assessment.

4.1. Limitations

Although our number of hemorrhagic strokes was higher than in most other studies in PLWHIV, [3,14] and our findings were broadly consistent with other published studies, both in the general population and in PLWHIV, the relatively small number of events may have reduced our power to detect clinically important differences in the predictive ability of risk factors, urging a conservative interpretation of our findings. As our primary interest was in the potential impact of uncontrolled hypertension, we did not investigate whether treated individuals with normalized BP might remain at higher risk of stroke. Analyses of treated hypertension in an international and multi-center cohort collaboration such as the D:A:D Study will be limited by variations in the diagnosis and treatment of hypertension, as well as the frequency of blood pressure monitoring, which are all likely to vary by country and clinic. For

this reason, our analyses deliberately considered a simple definition of hypertension based on a single elevated blood pressure assessment only. However, sensitivity analyses which considered a more conservative definition (based on the requirement for two consecutive blood pressure assessments to be elevated) reached similar conclusions. Unfortunately, we do not have access to information on the subtypes of any ischemic strokes which would permit us to undertake more precise risk estimation and we do not systematically collect some stroke risk factors such as atrial fibrillation, heart failure, alcohol abuse or inflammatory markers that may play a role in stroke risk. Despite extensive efforts to obtain complete data on HCV coinfection, this information is missing for a proportion of participants which may restrict our analyses of associations with this infection. Finally, as with any observational study, unmeasured or residual confounding may have influenced our findings.

In summary, the risk factor profiles for ischemic and hemorrhagic strokes in PLWHIV appear to differ. While we found no strong evidence to support the need for specific stroke risk prediction scores for PLWHIV, our findings do emphasize the importance of considering stratified stroke risk prediction for the different stroke subtypes to optimize preventive measures and screening. Further studies are needed to confirm our findings in order to provide more precise risk scoring systems in PLWHIV as well as in the general population.

Ethics Committee Approval

This analysis was conducted in accordance with the Declaration of Helsinki and approved by national ethical committee where necessary.

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Authors' Contributions

CIH had full access to all the data in the study and takes responsibility for the integrity of the data and analysis. CIH, LR, DK, JDL and CS developed the initial analysis protocol. CIH performed study co-ordination and prepared the datasets for analysis. DK and CS performed the statistical analyses. CIH prepared the first draft of the manuscript and completed all revisions. LR, JDL and CS provided critical input at all stages of the preparation of the manuscript. SDW, ML, AP, PR, ADM, AM, CP, OK, HK, WE-S and FB provided data and revised the manuscript critically. All authors have provided input at all stages of the project and approved the final version.

Declaration of Competing Interest

PR has served as a scientific adviser to Bristol-Myers Squibb, Gilead Sciences, Grupo Ferrer Internacional, GlaxoSmithKline, Janssen Pharmaceutica, Merck, and ViiV Healthcare; has served on data and safety monitoring boards and endpoint adjudication committees for Janssen Pharmaceutica; reports honoraria to his institution for speaking engagements at scientific conferences from Bristol-Myers Squibb, Gilead Sciences, and GlaxoSmithKline; and reports research support from Gilead Sciences, ViiV Healthcare, Merck, Janssen Pharmaceutica, Bristol-Myers Squibb, Abbott Laboratories, and Boehringer Ingelheim.

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CS reports grants from The D:A:D Oversight Committee, during the conduct of the study, personal fees from Gilead Sciences, personal fees from ViiV Healthcare, and personal fees from Janssen-Cilag, outside the submitted work.

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HK has received travel grants from Gilead and her institution received consultancy fees from Gilead and MSD; OK reports personal fees from Gilead, personal fees from MSD, personal fees from ViiV, non-financial support from Gilead, personal fees from Gilead, personal fees from Janssen, non-financial support from ViiV, and non-financial support from BMS, outside the submitted work; SDW.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eclinm.2019.07.008.

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