Cancer Risk and Use of Protease Inhibitor or Nonnucleoside Reverse Transcriptase Inhibitor–Based Combination Antiretroviral Therapy: The D:A:D Study

Mathias Bruyand, MD, PhD, Lene Ryom, MD, PhD,† Leah Shepherd, MBiostat,‡ Gerd Fatkenheuer, MD, PhD,§‖ Andrew Grulich, MD, PhD,¶ Peter Reiss, MD, PhD,#** Stéphane de Wit, MD, PhD,†† Antonella d'Arminio Monforte, MD, PhD,‡‡ Hansjakob Furrer, MD, PhD,§§ Christian Pradier, MD, PhD,‖‖ Jens Lundgren, MD, PhD,† and Caroline Sabin, PhD,‡ for the D:A:D study group*

Background: The association between combination antiretroviral therapy (cART) and cancer risk, especially regimens containing protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs), is unclear.

Methods: Participants were followed from the latest of D:A:D study entry or January 1, 2004, until the earliest of a first cancer diagnosis, February 1, 2012, death, or 6 months after the last visit. Multivariable Poisson regression models assessed associations between cumulative (per year) use of either any cART or PI/NNRTI, and the incidence of any cancer, non–AIDS-defining cancers (NADC), AIDS-defining cancers (ADC), and the most frequently occurring ADC (Kaposi sarcoma, non-Hodgkin lymphoma) and NADC (lung, invasive anal, head/neck cancers, and Hodgkin lymphoma).

Results: A total of 41,762 persons contributed 241,556 person-years (PY). A total of 1832 cancers were diagnosed [incidence rate: 0.76/100 PY (95% confidence interval: 0.72 to 0.79)], 718 ADC [0.30/100 PY (0.28–0.32)], and 1114 NADC [0.46/100 PY (0.43–0.49)]. Longer exposure to cART was associated with a lower ADC risk [adjusted rate ratio: 0.88/year (0.85–0.92)] but a higher NADC risk [1.02/year (1.00–1.03)]. Both PI and NNRTI use were associated with a lower ADC risk [PI: 0.96/year (0.92–1.00); NNRTI: 0.86/year (0.81–0.91)]. PI use was associated with a higher NADC risk [1.03/year (1.01–1.05)]. Although this was largely driven by an association with anal cancer [1.08/year (1.04–1.13)], the association remained after excluding anal cancers from the end point [1.02/year (1.01–1.04)]. No association was seen between NNRTI use and NADC [1.00/year (0.98–1.02)].

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From the *INSERM, ISPED, Centre Inserm U897-Epidemiologie-Biostatistique, Bordeaux, France; †Copenhagen HIV Programme, Department of Infectious Diseases and Rheumatology, Section 8632, Finsencenteret, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; ‡Research Department of Infection and Population Health, UCL, London, United Kingdom; §First Department of Internal Medicine, University Hospital of Cologne, Köln, Germany; ‖German Center for Infection research (DZIF); ¶HIV Epidemiology and Prevention Program, Kirby Institute, UNSW Australia, Sydney, Australia; #Division of Infectious Diseases and Department of Global Health, Amsterdam Institute for Global Health and Development, Academic Medical Center, Amsterdam, the Netherlands; **Stichting HIV Monitoring, Amsterdam, the Netherlands; ††Department of Infectious Diseases, St Pierre University Hospital, Brussels, Belgium; ‡‡Infectious Diseases Unit, Department of Health Sciences, San Paolo University Hospital, Milan, Italy; §§Department of Infectious Diseases, Bern University Hospital and University of Bern, Bern, Switzerland; and ‖‖Département de Santé Publique, Hôpital de l'Archet, CHU de Nice, Nice, France.

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Correspondence to: Mathias Bruyand, MD, PhD, Inserm U897, ISPED, case 11, 146 rue Léo Saignat, 33076 Bordeaux, France (e-mail: mathias.bruyand@gmail.com).

Conclusions: Cumulative use of PIs may be associated with a higher risk of anal cancer and possibly other NADC. Further investigation of biological mechanisms is warranted.

Key Words: HIV, cancer, risk, antiretroviral therapy

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INTRODUCTION

The widespread use of combination antiretroviral therapy (cART) beginning in the mid-1990s for persons living with HIV (PLWHIV) brought about dramatic improvements in health and survival. An increased risk of Kaposi sarcoma and non-Hodgkin lymphoma was already well recognized in PLWHIV, but the reduction in AIDS-related morbidity and mortality further revealed that some non–AIDS-defining cancers (NADC) were more frequent in this population.[1–3] Subsequently, as the availability of cART has increased, there has been a decline in the risk of AIDS-defining cancer (ADC) compared with levels seen in the pre-cART era. Although the aging of the population has resulted in an increase in the number of reported NADC events compared with the pre-cART era, reported reductions in the incidence of NADC have generally been smaller or nonexistent.[2,4]

The prevalence of traditional cancer risk factors, such as smoking, coinfection with hepatitis B and C viruses (HBV and HCV), and human papilloma virus (HPV), is higher in PLWHIV than that in the general population.[5–8] HIV-induced immune depression is a strong predictor of ADC and might also contribute to the risk of some NADC.[4,9,10] Although uncontrolled plasma HIV RNA viral load has been reported to be a risk factor for ADC,[9,10] its role in NADC (especially anal cancer) occurrence remains unclear.[10,11] Finally, inflammation might also contribute to cancer risk in this population.[12]

cART may directly affect the risk of cancer in PLWHIV through various biological pathways. The effects of cART on HIV RNA and CD4 count have a beneficial impact on the risk of cancer occurrence in cancers associated with viruses, such as Kaposi Sarcoma or polyclonal lymphocyte stimulation like NHL. But cART-associated immune reconstitution may also enhance the immune control of cancer development. However, cytochrome P450 (CYP450) for instance is known to be involved in cancer risk.[13] The long-term effect of cART on the CYP450 enzyme system may affect cancer risk by altering the excretion of various pro-oncogenic substances. Different effects of the protease inhibitor (PI) and nonnucleoside reverse transcriptase inhibitor (NNRTI) drug classes on cancer risk may be hypothesized, as different parts of the CYP450 system are inhibited and induced by PIs and induced by NNRTIs. In contrast, a direct antineoplastic effect of certain PI and NNRTI drugs has been suggested, although these potential effects have not been clearly assessed to date.[14,15]

Although an overall protective effect of cART on ADC risk has been seen in several clinical studies,[10,16–19] an association between cART use and NADC risk remains controversial. One study has reported an association with a higher NADC risk,[20] whereas others have not demonstrated such a relationship.[6,17,21] A recent large study reported that cART use was related to a lower risk of infection-unrelated NADC, but this association was not seen in all analyses performed.[18]

cART has been shown to have a protective effect on Kaposi sarcoma risk,[10,18] whereas the association between the risk of non-Hodgkin lymphoma and cART has not been clarified.[10,18,22–24] Compared with the general population, risks of liver and colorectal cancer and Hodgkin lymphoma have remained unchanged over time. In contrast, lung cancer risk may have decreased[2]; the risk of anal cancer initially increased when cART was introduced, and subsequently reached a plateau.[2,25] In this study, we aimed to assess the relationships between cART use overall, as well as PI and NNRTI use separately, and the risk of cancers among PLWHIV.

METHODS

The D:A:D study is a prospective study formed by the collaboration of 11 cohorts in Europe, Australia, and the United States.[26] All participating cohorts in D:A:D followed local national guidelines/regulations regarding patient consent and/or ethical review. Information on all AIDS events, including all ADCs, has been provided prospectively on an annual basis since the start of the study in 1999. Since 2008, information has also been collected on any NADC (any NADC other than basal or squamous cell skin cancer, precancers, and relapses). All participating cohorts have been collecting information prospectively on NADC from 2008 or earlier; information was also collected retrospectively on events occurring from January 1, 2004, to January 31, 2008. Detailed information on each NADC is collected on a specific case report form. All reported events (including all ADC and NADC) are validated centrally at the D:A:D coordinating center with a proportion of events selected for discussion with an external consultant oncologist. All events are regularly monitored for accuracy, and random monitoring is performed at participating centers to ensure complete ascertainment of events.

D:A:D participants were followed from the latest of January 1, 2004 (start of cancer data collection) or D:A:D study entry, until the earliest of a first incident cancer diagnosis (any type, excluding precancer stages), February 1, 2012, death, or 6 months after the last visit. As in previous analyses of the data set, each individual's follow-up was split into a series of consecutive 1-month periods and his/her age and clinical status (including exposure to cART, PI, and NNRTIs) at the start of each period was established. At the time of study entry, individuals may already have been exposed to cART, with exposure then accruing over follow-up.

Several outcomes were analyzed: first, any cancer diagnosis was analyzed as the outcome; second, NADC and ADC were analyzed separately; finally, each of the most frequently occurring ADC (Kaposi sarcoma, non-Hodgkin lymphoma) and NADC (lung cancer, invasive anal cancer, Hodgkin lymphoma, and head and neck cancer) were considered separately. In each analysis, follow-up of patients affected by a cancer other than the one of interest (eg, NADC in analyses of ADC) was right censored at the time of cancer diagnosis to avoid any bias that might be introduced through more frequent subsequent monitoring for cancer. Of note, screening for cervical cancer is well established in HIV-positive women. As a result, the incidence of cervical cancer is now relatively low in this population. Thus, we also performed

a sensitivity analysis in which cervical dysplasias were included with invasive cervical cancer. This sensitivity analysis excluded 3 cohorts (EuroSIDA, ICoNA, and Brussels St. Pierre) that do not routinely collect data on cervical dysplasias.

Poisson regression models were used to assess associations between the incidence of cancer and cumulative exposure to cART, defined as any regimen including a PI or NNRTI. Initial analyses considered associations with cumulative exposure to any cART, with subsequent models then considering associations with exposure to the PI and NNRTI classes separately. Treatment covariates were included as time-updated covariates, so an individual's treatment status with respect to exposure could change over time; reported adjusted rate ratio estimates are scaled to reflect the impact of each additional year of exposure on the outcome. Models were adjusted for gender, participating cohort, mode of HIV acquisition, ethnic group, any previous cancer (all as fixed covariates), age (as a continuous, time-updated covariate), calendar year, body mass index, previous AIDS diagnosis, HBV status, HCV status, and smoking status (all as time-updated covariates). Individuals were classified as HCV negative, unknown, or positive (HCV antibody positive and HCV RNA positive or unknown) and as HBV negative, unknown, or positive (HBV surface-antigen positive, HBV e antigen positive or HBV DNA positive, and HBV e antigen antibodies positive). Smoking status was defined as current, ex-smoker, never smoked, and unknown. Because of the potential role of the CD4 count as both a confounder for initiation of cART and a factor on the causal pathway between the initiation of cART and cancer development, our primary analyses did not include adjustment for the CD4 count.[27] However, sensitivity analyses considered whether conclusions were modified after adjusting for either the baseline or nadir (time updated) CD4 count. All analyses were performed using SAS software, version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 41,762 D:A:D participants were included, accounting for 241,556 person-years of follow-up [median, 6.5 years per person; interquartile range (IQR), 3.7–8.1]. Approximately, 3-quarters were male and the main mode of HIV acquisition was sex between men. At study entry, the median age was 39 years (IQR, 33–46), 40% of participants were current smokers, 6% had a history of cancer, and 4% and 10% were HBV and HCV coinfected, respectively; the median CD4 count was 433 cells per cubic millimeter (IQR, 281–620) and median plasma HIV RNA was 2.3 $\log_{10}$ copies per milliliter (IQR, 1.7–4.3) (Table 1). Over the course of follow-up, 37,472 participants were exposed to cART [median (IQR) exposure: 7.1 (3.8–11.4) years; total exposure: 284,004 person-years (PYRS)], 28,743 were exposed to PIs [4.9 (2.2–8.8) years; total exposure: 168,445 PYRS], and 28,674 were exposed to NNRTIs [3.8 (1.6–7.4) years; total exposure: 136,434 PYRS]. Loss to follow-up rates in the cohort are 2%–3% in any particular year.

Over the study period, 1832 cancers were diagnosed [incidence rate (IR), 0.76/100 person-years; 95% confidence interval (CI): 0.72 to 0.79]; 718 were ADC [0.30 (0.27–0.32)], and 1114 were NADC [0.46 (0.43–0.49)]. The IR for ADC decreased as the duration of cART exposure increased, whereas an opposite trend was observed for NADC (Fig. 1).

The most frequent ADC was Kaposi sarcoma [341 cases; 0.14 (0.13–0.16)] followed by non-Hodgkin lymphoma [321 cases; 0.13 (0.12–0.15)]; only 56 cases of cervical cancer were reported [0.02/100 person-years (0.02–0.03), 0.09 (0.06–0.11) among women]. Among the NADC, lung cancer [195 cases; 0.08 (0.07–0.09)], anal cancer [131 cases; 0.05 (0.04–0.06)], Hodgkin lymphoma [107 cases; 0.04 (0.04–0.05)], and head and neck cancer [97 cases; 0.04 (0.03–0.05)] were most frequently observed.

Associations Between Cancer Incidence and cART Exposure

Overall, there was no association between exposure to cART and the rate of cancer [adjusted rate ratio 0.99 per

TABLE 1. Baseline Characteristics of the 41,762 Patients Eligible in the D:A:D Study

No. patients	41,762	100%
Gender, n (%)		
Male	30,564	73.2
Female	11,186	26.8
Unknown	12	0.0
Age, median (IQR), yrs	39 (33–46)	
Mode of acquisition, n (%)		
Sex between men	18,307	43.8
Intravenous drug users	6047	14.5
Heterosexual	14,715	35.2
Other/unknown	2693	6.5
Ethnic group, n (%)		
White	20,828	49.9
Black African	2919	7.0
Other	836	2.0
Unknown	17,179	41.1
Smoking status, n (%)		
Current smoker	16,607	39.8
Ex-smoker	7370	17.7
Never smoker	10,382	24.8
Unknown	7403	17.7
CD4 count, median (IQR), cells/mm^3	433 (281–620)	
Plasma HIV RNA, median (IQR), $\log_{10}$ copies/mL	2.3 (1.7–4.3)	
Hepatitis C virus status, n (%)		
Negative	26,305	63.0
Positive	4392	10.5
Unknown	11,065	26.5
Hepatitis B virus status, n (%)		
Negative	27,561	66.0
Positive	1767	4.2
Unknown	12,434	29.8
Previous cancer (AIDS and non-AIDS defining), n (%)	2346	5.6
Any exposure to cART, n (%)	37,472	89.7
Years of exposure, median (IQR)	7.1 (3.8–11.4)	
Any exposure to PIs, n (%)	28,743	68.8
Years of exposure, median (IQR)	4.9 (2.2–8.8)	
Any exposure to NNRTIs, n (%)	28,674	68.7
Years of exposure, median (IQR)	3.8 (1.6–7.4)	

IQR, interquartile range.

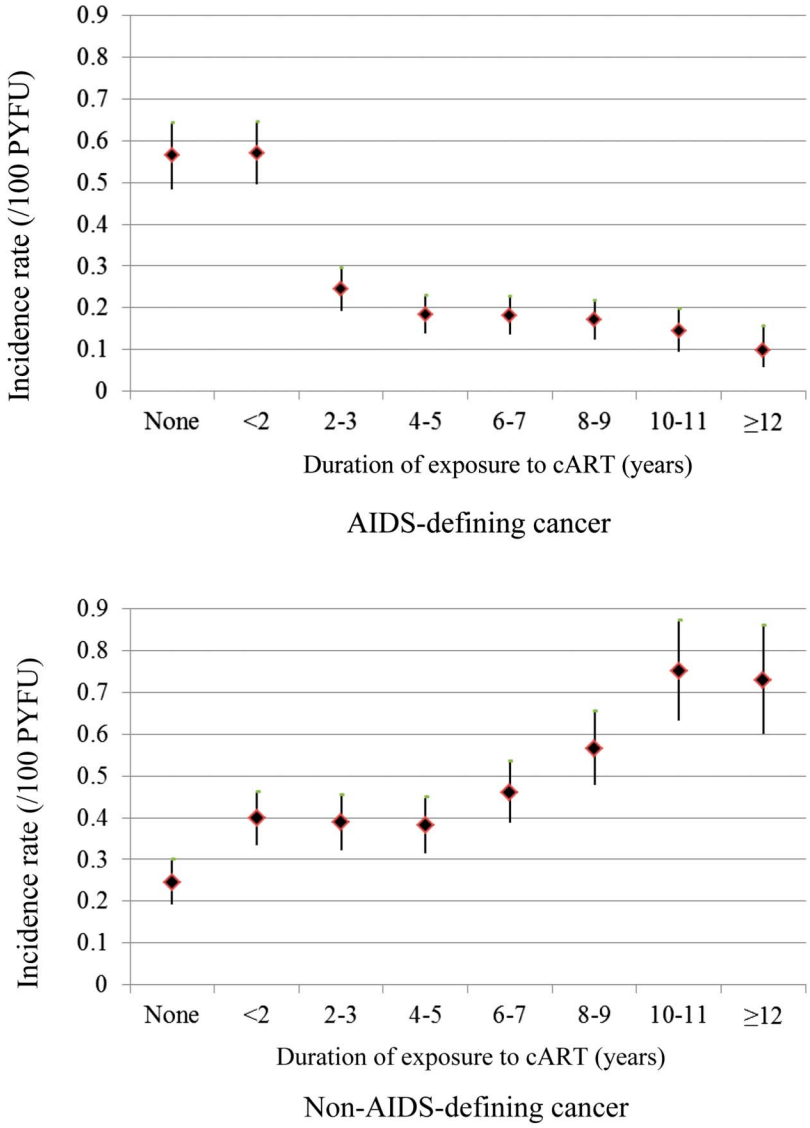

FIGURE 1. Incidence of ADC and NADC stratified by the duration of exposure to cART in years, the D:A:D study.

year (95% CI: 0.98 to 1.01), $P = 0.44$]. However, when considering the PI and NNRTI classes separately, different trends were seen, with exposure to the NNRTI class being associated with a reduction in cancer risk [0.98 per year (0.96–1.00), $P = 0.04$], but exposure to the PI class being associated with an increased risk [1.02 per year (1.00–1.03), $P = 0.02$].

When grouping cancers as either ADC or NADC, exposure to cART was associated with decreased ADC risk [0.88 per year, (0.85–0.92)] (Table 2) but an increased NADC risk [1.02 per year, (1.00–1.03)] (Table 3). Exposure to the PI and NNRTI drug classes were both associated with a lower risk of ADC [PI: 0.96 per year, (0.92–1.00); NNRTI: 0.86 per year, (0.81–0.91)] (Table 2). The association between cART exposure and a higher NADC risk seemed to be driven by exposure to PIs [1.03 per year, (1.01–1.05)] rather than to NNRTIs [1.00 per year, (0.98–1.02)] (Table 3).

Associations Between Incidence of Specific Cancer Types and PI/NNRTI Exposure

Exposure to both PI and NNRTI drug classes was related to a lower risk of Kaposi sarcoma [PI: 0.93 per year, (0.87–1.00); NNRTI: 0.81 per year, (0.74–0.90)]. NNRTI exposure was associated with a lower non-Hodgkin lymphoma risk [0.87 per year, (0.80–0.94)], but no association was seen with exposure to PI [0.98 per year, (0.93–1.04)] (Table 2).

PI use was associated with a higher risk of anal cancer [1.08 per year, (1.04–1.13)], whereas no such association was seen with NNRTI exposure [1.03 per year, (0.97–1.09)]. The association between PI exposure and anal cancer risk remained significant (and of similar size) in analyses that included adjustment for either the baseline [1.09 per year (1.05–1.14), $P = 0.0001$] or nadir [1.09 per year (1.04–1.14), $P = 0.0002$] CD4 count. In a sensitivity analysis that excluded anal cancers from the category of NADC, PI exposure

TABLE 2. Adjusted Rate Ratios (aRRs) for Associations Between cART Use (per Year Longer Exposure, Any cART or Whether PI or NNRTI Based) and ADC (Any Cancer and Specific Cancers), the D:A:D Study

	ADC (n = 718)			Kaposi Sarcoma (n = 341)			Non-Hodgkin Lymphoma (n = 321)		
	aRR*	95% CI	*P*	aRR	95% CI	*P*	aRR	95% CI	*P*
Any cART	0.88	0.85 to 0.92	0.0001	0.84	0.78 to 0.89	0.0001	0.90	0.85 to 0.95	0.0003
PI-based cART	0.96	0.92 to 1.00	0.05	0.93	0.87 to 1.00	0.04	0.98	0.93 to 1.04	0.53
NNRTI-based cART	0.86	0.81 to 0.91	0.0001	0.81	0.74 to 0.90	0.0001	0.87	0.80 to 0.94	0.0006

*aRR: adjusted rate ratio (adjusted for age, gender, cohort, mode of HIV acquisition, ethnic group, calendar year, body mass index, any previous cancer, previous AIDS diagnosis, smoking status, and HCV and HBV status).

ADC, AIDS-defining cancer; CI, confidence interval; cART, combination antiretroviral therapy; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

remained associated with an increased risk of cancer [1.02 per year (1.01–1.04), $P = 0.008$], suggesting that the association between PI use and NADC risk is not driven solely by the association seen with anal cancer.

Although NNRTI exposure was associated with a lower risk of Hodgkin lymphoma [0.90 per year, (0.82–0.99)], no association was seen between PI exposure and this cancer risk [0.99 per year, (0.92–1.06)] (Table 3).

Neither PI nor NNRTI exposure was associated with either lung or head and neck cancer risks (all $P \geq 0.23$) (Table 3).

In the sensitivity analysis that additionally included cervical dysplasias along with cervical cancers (based on 6 of the 9 participating cohorts), there were a total of 414 cervical cancer/dysplasia events over 35,804 person-years in women [IR, 1.16/100 person-years (1.05–0.30)]. There were strong associations between the combined cervical cancer/dysplasia end point and exposure to cART overall [0.82 per year (0.77–0.87), $P = 0.0001$] as well as to both PIs [0.86 per year (0.81–0.93), $P = 0.0001$] and NNRTIs [0.80 per year (0.73–0.87), $P = 0.0001$].

DISCUSSION

In this large international cohort of PLWHIV, each additional year of exposure to NNRTI-based cART was associated with a 2% reduction in cancer risk; this effect was driven by a reduction in the risk of ADC in those exposed to NNRTIs. In contrast, each additional year of exposure to PI-based cART was associated with a 2% increase in cancer risk, this association being driven by an increase in NADC risk in those exposed to PIs. Our finding of an overall increase in the risk of NADC with longer exposure to cART is consistent with a recent study, which described an increasing incidence of NADC with time on cART.[28] Our findings must be interpreted in the context of lifelong exposure to cART; if the association is causal, then exposure to PIs for 5 years, say, would result in increases in the risk of NADC of around 16%, respectively, suggesting that this may be clinically relevant in the case of long-term exposure to cART.

Since the mid-1990s, the risk of specific ADC has decreased in settings where cART is available.[2] Regarding NADC, 1 study found that a higher Hodgkin lymphoma risk was associated with NNRTI exposure,[20] 2 recent studies showed that PI exposure was associated with a higher anal cancer risk (although findings were not robust in sensitivity analyses),[18,29] and several studies have not reported any association between cART exposure and anal cancer risk.[10,20,30]

In our study, although use of an NNRTI-based cART regimen was consistently associated with a reduced risk of both Kaposi sarcoma and non-Hodgkin lymphoma, use of PI-based cART was only associated with a reduced risk of Kaposi sarcoma, but not of non-Hodgkin lymphoma, although the 95% CI for the latter association was wide and did not allow us to rule out the possibility of a beneficial effect on this outcome. Similarly, although an association between the PI class and an increased risk of NADC was statistically significant only for anal cancer, an increased risk with longer exposure to the class cannot be ruled out for the other 3 NADC considered. Of note, the association between PI use and anal cancer risk has now

TABLE 3. Adjusted Rate Ratios (aRRs) for Associations Between cART Use (per Year Longer Exposure, Any cART or Whether PI or NNRTI Based) and NADC (Any Cancer and Specific Cancers), the D:A:D Study

	NADC (n = 1114)			Lung Cancer (n = 195)			Anal Cancer (n = 131)			Hodgkin Lymphoma (n = 107)			Head and Neck Cancer (n = 97)		
	aRR*	95% CI	*P*	aRR	95% CI	*P*	aRR	95% CI	*P*	aRR	95% CI	*P*	aRR	95% CI	*P*
Any cART	1.02	1.00 to 1.03	0.04	0.99	0.95 to 1.03	0.64	1.06	1.01 to 1.11	0.03	0.91	0.85 to 0.97	0.005	1.01	0.96 to 1.07	0.68
PI-based cART	1.03	1.01 to 1.05	0.0002	1.01	0.97 to 1.05	0.57	1.08	1.04 to 1.13	0.0005	0.99	0.92 to 1.06	0.70	1.01	0.96 to 1.07	0.62
NNRTI-based cART	1.00	0.98 to 1.02	0.84	0.97	0.93 to 1.02	0.23	1.03	0.97 to 1.09	0.36	0.90	0.82 to 0.99	0.03	1.03	0.97 to 1.10	0.32

*aRR: adjusted rate ratio (adjusted for age, gender, cohort, mode of HIV acquisition, ethnic group, calendar year, body mass index, any previous cancer, previous AIDS diagnosis, smoking status, and HCV and HBV status).

CI, confidence interval; cART, combination antiretroviral therapy; PI, protease inhibitor; NADS, Non AIDS-Defining cancer; NNRTI, non-nucleoside reverse transcriptase inhibitor.

been confirmed in 3 different large and heterogeneous cohorts, including our study.[18,29]

Anal cancer incidence is higher in PLWHIV than that in the general population; this might be partly explained by the higher prevalence of anal HPV exposure and infection in PLWHIV. In addition, the longer survival of PLWHIV associated with cART may allow the expression of HPV's oncogenic potential.[31] Although some countries have initiated screening policies for anal cancer, which may lead to a higher detection rate overall, there is no obvious reason for the application of anal cancer screening policies to differ in those receiving PI- and NNRTI-based cART, and therefore, this is unlikely to explain the different associations seen between anal cancer risk and these 2 drug classes. A higher risk of anal cancer after initiation of cART due to immune reconstitution inflammatory syndrome is unexpected, as anal cancer is not generally reported in the context of immune reconstitution inflammatory syndrome.[32] Although we were unable to assess specific associations with cervical cancer due to a low number of events, our sensitivity analyses that additionally included cervical dysplasias into the end point revealed a very strong protective effect of both PI and NNRTI for the combined end point of cervical cancer or dysplasia. The association between cART and invasive cervical cancer will be assessed when a sufficient number of events have accrued.

The effect of cART on AIN risk remains controversial.[33,34] HPV is highly prevalent in this population, especially in men who have sex with men.[35,36] Further investigations that consider HPV coinfection and assess the effect of cART on both anal dysplasia and invasive cancer are required to explore a possible biological effect of PI on anal cancer risk. There is a need to assess the efficiency of anal cancer screening policies,[37] and the potential protective effect of HPV vaccination.[38] Although more rigorous application of AIN screening policies might look desirable in this population, particularly in those receiving a PI-based regimen,[39] it should be noted that the evidence of screening benefits on anal cancer remain unclear.[39]

Importantly, when all other NADCs than anal cancer were grouped, a signal associated with use of PI-based cART was still found, suggesting that among NADC, the risk of other individual cancers may also be related to cumulative PI exposure.

The risks of lung and head and neck cancer did not seem to be affected by PI or NNRTI exposure; these negative findings are unlikely to reflect low statistical power, as we did not see any nonsignificant trends in associations. Further analyses to investigate possible associations between other individual NADCs and the use of PIs will be performed in D:A:D once additional events have accrued, such as analyses investigating the association between specific drugs in the PI and NNRTI classes and cancer risk.

This is the first study to assess the role of PI- and NNRTI-based cART on cancer occurrence in a prospective international observational cohort validating centrally cancer end points. Cancer almost always result in hospitalization, information on which is generally passed back to cohorts, and according to the annual monitoring procedures applied in the D:A:D study, we do not believe that our cancer rates are underreported.

Several limitations of our study should be acknowledged. First, unmeasured confounding cannot be ruled out due to the observational design of the study. Lifestyle factors and viral infections may affect cancer risk, of which we are only able to adjust for smoking, HBV, and HCV status. We do, however, believe that this is an unlikely explanation for our findings of a higher risk of cancer with longer duration of PI exposure, as it would require a selective choice of PI-based cART in persons already at higher risk of cancer, which seems somewhat implausible. Although data on HPV coinfection are not captured in the study, our participating clinicians reported that knowledge of HPV status (where measured) is unlikely to influence the choice of cART regimen in an individual, and thus we do not believe that this would act as a confounder. Although it is theoretically possible that the results may be explained by differential CD4 responses to PIs and NNRTIs, findings from sensitivity analyses that controlled for the latest CD4 count were similar, suggesting that this is an unlikely possibility. It is possible that our findings could be explained by survivor bias as individuals who were on cART for longer periods of time would tend to be older and more likely to develop cancer as a result. However, our analyses were adjusted for age (as a continuous time-updated covariate). Furthermore, despite a similar age distribution among those receiving PIs and NNRTIs for prolonged periods of time, the quantitatively different associations reported for PIs and NNRTIs argue against increasing age as an explanation for our findings. Finally, because of the small numbers of specific types of NADCs, our analyses necessitated the combination of different types of cancer into a single end point, and thus, interpretation of our findings should be made with caution. Although this is not ideal, particularly, when addressing questions around etiology, use of a combined end point does allow some questions to be addressed regarding the overall incidence of cancer and contribution of cART (and cART classes) to its development.

In conclusion, our results suggest that cumulative use of PIs could be associated with a higher risk of invasive anal cancer, and possibly other NADC. We believe that further investigations are now justified to explore possible biological mechanisms for these findings. In the absence of such studies, and in the context of aging population increasingly exposed to PI-containing cART regimens, continued efforts should be put into the prevention of NADC, particularly anal cancer.

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APPENDIX 1

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 #.

Members of the D:A:D SC From the Oversight Committee

B. Powderly*, N. Shortman*, C. Moecklinghoff *, G. Reilly*, and X. Franquet*.

D:A:D Central Coordination

L. Ryom, C. A. Sabin*, D. Kamara, C. Smith, A. Phillips*, A. Mocroft, J. Tverland, M. Mansfeld, J. Nielsen, D. Raben, and J. D. Lundgren#.

D:A:D Data Managers

R. Salbøl Brandt (coordinator), M. Rickenbach, I. Fanti, E. Krum, M. Hillebregt, S. Geffard, A. Sundström, M. Delforge, E. Fontas, F. Torres, H. McManus, S. Wright, and J. Kjær.

Verification of End points

A. Sjøl (CVD primary end point), P. Meidahl (oncology, new end point), J. Helweg-Larsen (hematology, new end point), and J. Schmidt Iversen (nephrology, new end point).

Kidney Working Group

L. Ryom, A. Mocroft, O. Kirk*, P. Reiss*, M. Ross, C. A. Fux, P. Morlat, O. Moranne, A. M. Kesselring, D. A. Kamara, C. Smith, and J. D. Lundgren#.

Mortality Working Group

C. Smith, L. Ryom, A. Phillips*, R. Weber*, P. Morlat, C. Pradier*, P. Reiss*, N. Friis-Møller, J. Kowalska, and J. D. Lundgren#.

Cancer Working Group

C. Sabin*, M. Law*, A. d'Arminio Monforte*, F. Dabis*, M. Bruyand, P. Reiss*, C. Smith, D. A. Kamara, M. Bower, G. Fätkenheuer, A. Donald, A. Grulich, L. Ryom, and J. D. Lundgren#.

Members of the 11 Cohorts

ATHENA (AIDS Therapy Evaluation Project Netherlands)

Central coordination: P. Reiss*, S. Zaheri, M. Hillebregt, and L. Gras.

Participating physicians (¤Site coordinating physicians): Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam: Prof. Dr. J. M. Prins, Prof. Dr. T. W. Kuijpers, Dr. H. J. Scherpbier, Dr. J. T. M. van der Meer, Dr. F. W. M. N. Wit, Dr. M. H. Godfried, Prof. Dr. P. Reiss*, Prof. Dr. T. van der Poll, Dr. F. J. B. Nellen, Prof. Dr. J. M. A. Lange, Dr. S. E. Geerlings, Dr. M. van Vugt, Dr. D. Pajkrt, Drs. J. C. Bos, Drs. M. van der Valk, Drs. M. L. Grijsen, Dr. W. J. Wiersinga, Dr. A. Goorhuis, Dr. J. W. R. Hovius. Academisch Ziekenhuis Maastricht, Maastricht: Dr. S. Lowe, Dr. A. Oude Lashof, Dr. D. Posthouwer. Catharina-ziekenhuis, Eindhoven: Drs. M. J. H. Pronk, Dr. H. S. M. Ammerlaan. Erasmus Medisch Centrum, Rotterdam: Dr. M. E. van der Ende, Dr. T. E. M. S. de Vries-Sluijs, Dr. C. A. M. Schurink, Dr. J. L. Nouwen, Dr. A. Verbon, Drs. B. J. A. Rijnders, Dr. E. C. M. van Gorp, Drs. M. van der Feltz. Erasmus Medisch Centrum–Sophia, Rotterdam: Dr. G. J. A. Driessen, Dr. A. M. C. van Rossum. Flevoziekenhuis. Almere: Dr. J. Branger. HagaZiekenhuis, Den Haag: Dr. E. F. Schippers, Dr. C. van Nieuwkoop, Drs. E. P. van Elzakker. Isala Klinieken, Zwolle: Dr. P. H. P. Groeneveld, Drs. J. W. Bouwhuis. Kennemer Gasthuis: Drs. R. Soetekouw, Prof. Dr. R. W. ten Kate. Leids Universitair Medisch Centrum, Leiden: Dr. F. P. Kroon, Prof. Dr. J. T. van Dissel, Dr. S. M. Arend, Dr. M. G. J. de Boer, Drs. H. Jolink, Dr. H. J. M. ter Vollaard, Drs. M. P. Bauer. Maasstadziekenhuis, Rotterdam: Dr. J. G. den Hollander, Dr. K. Pogany. Medisch Centrum Alkmaar, Alkmaar: Drs. G. van Twillert, Drs. W. Kortmann, Dr. J. W. T. Cohen Stuart, Dr. B. M. W. Diederen. Medisch Centrum Haaglanden, Den Haag: Dr. E. M. S. Leyten, Dr. L. B. S. Gelinck. Medisch Spectrum Twente, Enschede: Drs. G. J. Kootstra, Drs. C. E. Delsing. Onze Lieve Vrouwe Gasthuis, Amsterdam: Prof. Dr. K. Brinkman, Dr. W. L. Blok, Dr. P. H. J. Frissen, Drs. W. E. M. Schouten, Drs. G. E. L. van den Berk. Sint Elisabeth Ziekenhuis, Tilburg: Dr. M. E. E. van Kasteren, Dr. A. E. Brouwer. Sint Lucas Andreas Ziekenhuis, Amsterdam: Dr. J. Veenstra, Dr. K. D. Lettinga. Slotervaartziekenhuis, Amsterdam: Dr. J. W. Mulder, Drs. S. M. E. Vrouenraets, Dr. F. N. Lauw. Stichting Medisch Centrum Jan van Goyen, Amsterdam: Drs. A. van Eeden, Dr. D. W. M. Verhagen. Universitair Medisch Centrum Groningen, Groningen: Drs. H. G. Sprenger, Drs. R. Doedens, Dr. E. H. Scholvinck, Dr. S. van Assen, Dr. W. F. W. Bierman. Universitair Medisch Centrum Sint Radboud, Nijmegen: Dr. P. P. Koopmans, Dr. M. Keuter, Dr. A. J. A. M. van der Ven, Dr. H. J. M. ter Hofstede, Dr. A. S. M. Dofferhoff, Dr. A. Warris, Dr. R. van Crevel. Universitair Medisch Centrum Utrecht, Utrecht: Prof. Dr. A. I. M. Hoepelman, Dr. T. Mudrikova, Dr. M. M. E. Schneider, Dr. P. M. Ellerbroek, Dr. J. J. Oosterheert, Dr. J. E. Arends, Dr. M. W. M. Wassenberg, Dr. R. E. Barth. Vrije Universiteit Amsterdam, Amsterdam: Dr. M. A. van Agtmael, Dr. R. M. Perenboom, Drs. F. A. P. Claessen, Dr. M. Bomers, Dr. E. J. G. Peters. Wilhelmina Kinderziekenhuis, Utrecht: Dr. S. P. M. Geelen, Dr. T. F. W. Wolfs, Dr. L. J. Bont. Ziekenhuis Rijnstate, Arnhem: Dr. C. Richter, Dr. J. P. van der Berg, Dr. E. H. Gisolf. Admiraal De Ruyter Ziekenhuis, Vlissingen: Drs. M. van den Berge, Drs. A. Stegeman. Medisch Centrum Leeuwarden, Leeuwarden: Dr. M. G. A. van Vonderen, Drs. D. P. F. van Houte. Medisch Centrum Zuiderzee, Lelystad: Dr. S. Weijer, Dr. R. el Moussaoui. Sint Elisabeth Hospital, Willemstad—Curaçao: Dr. C. Winkel, Dr. F. Muskiet, Dr. Durand, and Dr. R. Voigt.

Aquitaine Cohort (France)

Principal investigator: Pr. F. Dabis*.

Scientific committee: Profs. F. Bonnet, D. Breilh, F. Dabis*, M. Dupon, G. Chêne, H. Fleury, D. Malvy, P. Mercié, I. Pellegrin, P. Morlat, D. Neau, J. L. Pellegrin, and R. Thiébaut; Drs. S. Bouchet, V. Gaborieau, D. Lacoste, and S. Tchamgoué.

Composition of the GECSA: Epidemiology and biostatistics: Profs. G. Chêne, F. Dabis, and R. Thiébaut; Drs. M. Bruyand, S. Lawson-Ayayi, and L. Wittkop.

Clinical and biological hospital units: Bordeaux University Hospital: Prof. P. Morlat (Prof. F. Bonnet, Drs. N. Bernard, M. Hessamfar, D. Lacoste, M. A. Vandenhende); Prof. M. Dupon (Drs. F. A. Dauchy, H. Dutronc), Prof. M. Longy-Boursier (Prof. P. Mercié, Drs. P. Duffau, J. Roger Schmeltz), Prof. D. Malvy (Drs. T. Pistone, M. C. Receveur), Prof. D. Neau (Drs. C. Cazanave, A. Ochoa, M. O. Vareil), Prof. J. L. Pellegrin (Prof. J. F. Viallard, Drs. C. Greib, E. Lazaro); Prof. H. Fleury (Prof. M. E. Lafon, Drs. S. Reigadas, P. Trimoulet); Prof. D. Breilh; Prof. M. Molimard (Drs. S. Bouchet, K. Titier); Prof. J. F. Moreau (Dr. I. Pellegrin); Drs. F. Haramburu, G. Miremont-Salamé. Arcachon Hospital: Dr. A. Dupont. Dax Hospital: Dr. Y. Gerard (Drs. L. Caunègre, K. André). Bayonne Hospital: Dr. F. Bonnal (Drs. S. Farbos, M. C. Gemain). Libourne Hospital: Dr. J. Ceccaldi (Dr. S. Tchamgoué). Mont-de-Marsan Hospital: Dr. S. De Witte (Dr. C. Courtault). Pau Hospital: Drs. E. Monlun (Dr. V. Gaborieau). Périgueux Hospital: Dr. P. Lataste (Dr. J. P. Meraud). Villeneuve-sur-Lot Hospital: Dr. I. Chossat.

Permanent team: M. J. Blaizeau, M. Bruyand, V. Conte, M. Decoin, J. Delaune, S. Delveaux, F. Diarra, C. D'Ivernois, A. Frosch, S. Geffard, C. Hanappier, S. Lawson-Ayayi, E. Lenaud, O. Leleux, F. Le Marec, J. Leray, I. Louis, G. Palmer, A. Pougetoux, X. Sicard, D. Touchard, and B. Uwamaliya-Nziyumvira.

AHOD (Australian HIV Observational Database, Australia)

Central coordination: M. Law*, K. Petoumenos, H. McManus, S. Wright, C. Bendall (Sydney, New South Wales).

Participating physicians (city, state): R. Moore, S. Edwards, J. Hoy, K. Watson, N. Roth, J. Nicholson (Melbourne, VIC); M. Bloch, T. Franic, D. Baker, R. Vale, A. Carr, D. Cooper (Sydney, New South Wales); J. Chuah, M. Ngieng (Gold Coast, Queensland), D. Nolan, J. Skett (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).

The Brussels St Pierre Cohort (Belgium): Coordination: S. De Wit*, N. Clumeck, M. Delforge, and C. Necsoi. Participating physicians: N. Clumeck, S. De Wit*, A. F. Gennotte, M. Gerard, K. Kabeya, D. Konopnicki, A. Libois, C. Martin, M. C. Payen, P. Semaille, and Y. Van Laethem.

CPCRA (USA)

Central coordination: J. Neaton, G. Bartsch, W. M. El-Sadr*, E. Krum, G. Thompson, D. Wentworth.

Participating physicians (city, state): R. Luskin-Hawk (Chicago, IL); E. Telzak (Bronx, NY); W. M. El-Sadr (Harlem, NY); D. I. Abrams (San Francisco, CA); D. Cohn (Denver, CO); N. Markowitz (Detroit, MI); R. Arduino (Houston, TX); D. Mushatt (New Orleans, LA); G. Friedland (New Haven, CT); G. Perez (Newark, NJ); E. Tedaldi (Philadelphia, PA); E. Fisher (Richmond, VA); F. Gordin (Washington, DC); L. R. Crane (Detroit, MI); J. Sampson (Portland, OR); J. Baxter (Camden, NJ).

EuroSIDA (Multinational)

Coordinating Center: J. Lundgren#, O. Kirk*, A. Mocroft, A. Cozzi-Lepri, D. Grint, D. Podlekareva, J. Kjær, L. Peters, J. Reekie, J. Kowalska, J. Tverland, A. H. Fischer, J. Nielsen.

Participating Countries and Physicians—Argentina: (M. Losso), C. Elias, Hospital JM Ramos Mejia, Buenos Aires.

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

Belarus: (I. Karpov), A. Vassilenko, Belarus State Medical University, Minsk, V. M. Mitsura, Gomel State Medical University, Gomel; O. Suetnov, Regional AIDS Centre, Svetlogorsk.

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

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

Bulgaria: (K. Kostov), Infectious Diseases Hospital, Sofia.

Croatia: (J. Begovac), University Hospital of Infectious Diseases, Zagreb.

Czech Republic: (L. Machala), D. Jilich, Faculty Hospital Bulovka, Prague; D. Sedlacek, Charles University Hospital, Plzen.

Denmark: (J. Nielsen), G. Kronborg, T. Benfield, M. Larsen, Hvidovre Hospital, Copenhagen; J. Gerstoft, T. Katzenstein, A-B. E. Hansen, P. Skinhøj, Rigshospitalet, Copenhagen; C. Pedersen, Odense University Hospital, Odense; L. Ostergaard, Skejby Hospital, Aarhus.

Estonia: (K. Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve.

Finland: (M. Ristola), Helsinki University Central Hospital, Helsinki.

France: (C. Katlama), Hôpital de la Pitié-Salpétière, Paris; J-P. Viard, Hôpital Necker-Enfants Malades, Paris; P-M. Girard, Hospital Saint-Antoine, Paris; J. M. Livrozet, Hôpital Edouard Herriot, Lyon; P. Vanhems, University Claude Bernard, Lyon; C. Pradier, Hôpital de l'Archet, Nice; F. Dabis*, D. Neau, Unité INSERM, Bordeaux. Germany: (J. Rockstroh), Universitäts Klinik Bonn; R. Schmidt, Medizinische Hochschule Hannover; J. van Lunzen, O. Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; H. J. Stellbrink, IPM Study Center, Hamburg; S. Staszewski, J. W. Goethe University Hospital, Frankfurt; Markus Bickel, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne.

Greece: (J. Kosmidis), P. Gargalianos, G. Xylomenos, J. Perdios, Athens General Hospital; G. Panos, A. Filandras, E. Karabatsaki, first IKA Hospital; H. Sambatakou, Ippokration General Hospital, Athens.

Hungary: (D. Banhegyi), Szent Lásló Hospital, Budapest.

Ireland: (F. Mulcahy), St. James Hospital, Dublin.

Israel: (I. Yust), D. Turner, M. Burke, Ichilov Hospital, Tel Aviv; S. Pollack, G. Hassoun, Rambam Medical Center, Haifa; S. Maayan, Hadassah University Hospital, Jerusalem.

Italy: (S. Vella), Istituto Superiore di Sanità, Rome; R. Esposito, I. Mazeu, C. Mussini, Università Modena, Modena; C. Arici, Ospedale Riuniti, Bergamo; R. Pristera, Ospedale Generale Regionale, Bolzano; F. Mazzotta, A. Gabbuti, Ospedale S. Maria Annunziata, Firenze; V. Vullo, M. Lichtner, University di Roma la Sapienza, Rome; A. Chirianni, E. Montesarchio, M. Gargiulo, Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; G. Antonucci, A. Testa, P. Narciso, C. Vlassi, M. Zaccarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A. Lazzarin, A. Castagna, N. Gianotti, Ospedale San Raffaele, Milan; M. Galli, A. Ridolfo, Osp. L. Sacco, Milan; A d'Arminio Monforte*, Istituto Di Clinica Malattie Infettive e Tropicale, Milan.

Latvia: (B. Rozentale), I. Zeltina, Infectology Centre of Latvia, Riga.

Lithuania: (S. Chaplinskas), Lithuanian AIDS Centre, Vilnius.

Luxembourg: (R. Hemmer), T. Staub, Centre Hospitalier, Luxembourg.

Netherlands: (P. Reiss*), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam.

Norway: (V. Ormaasen), A. Maeland, J. Bruun, Ullevål Hospital, Oslo.

Poland: (B. Knysz) J. Gasiorowski, Medical University, Wroclaw; A. Horban, E. Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; A. Grzeszczuk, R. Flisiak, Medical University, Bialystok; A. Boron-Kaczmarska, M. Pynka, M. Parczewski, Medical University, Szczecin; M. Beniowski, E. Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H. Trocha, Medical University, Gdansk; E. Jablonowska, E. Malolepsza, K. Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz.

Portugal: (F. Antunes), M. Doroana, L. Caldeira, Hospital Santa Maria, Lisbon; K. Mansinho, Hospital de Egas Moniz, Lisbon; F. Maltez, Hospital Curry Cabral, Lisbon.

Romania: (D. Duiculescu), Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucarest.

Russia: (A. Rakhmanova), Medical Academy Botkin Hospital, St Petersburg; N. Zakharova, St Petersburg AIDS Centre, St Peterburg; S. Buzunova, Novgorod Centre for AIDS, Novgorod.

Serbia: (D. Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade.

Slovakia: (M. Mokráš), D. Staneková, Dérer Hospital, Bratislava.

Slovenia: (J. Tomazic), University Clinical Centre Ljubljana, Ljubljana.

Spain: (J. González-Lahoz), V. Soriano, P. Labarga, J. Medrano, Hospital Carlos III, Madrid; S. Moreno, J. M. Rodriguez, Hospital Ramon y Cajal, Madrid; B. Clotet, A. Jou, R. Paredes, C. Tural, J. Puig, I. Bravo, Hospital Germans Trias i Pujol, Badalona; J. M. Gatell, J. M. Miró, Hospital Clinic i Provincial, Barcelona; P. Domingo, M. Gutierrez, G. Mateo, M. A. Sambeat, Hospital Sant Pau, Barcelona.

Sweden: (A. Karlsson), Venhaelsan-Sodersjukhuset, Stockholm; L. Flamholc, Malmö University Hospital, Malmö.

Switzerland: (B. Ledergerber), R. Weber*, University Hospital, Zürich; P. Francioli, M. Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B. Hirschel, E. Boffi, Hospital Cantonal Universitaire de Geneve, Geneve; H. Furrer, Inselspital Bern, Bern; M. Battegay, L. Elzi, University Hospital Basel.

Ukraine: (E. Kravchenko), N. Chentsova, Kiev Centre for AIDS, Kiev; V. Frolov, G. Kutsyna, Luhansk State Medical University; Luhansk; S. Servitskiy, Odessa Region AIDS Center, Odessa; M. Krasnov, Kharkov State Medical University, Kharkov.

United Kingdom: (S. Barton), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; A. M. Johnson, D. Mercey, Royal Free and University College London Medical School, London (University College Campus); A. Phillips, M. A. Johnson, A. Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); M. Murphy, Medical College of Saint Bartholomew's Hospital, London; J. Weber, G. Scullard, Imperial College School of Medicine at St. Mary's, London; M. Fisher, Royal Sussex County Hospital, Brighton; C. Leen, Western General Hospital, Edinburgh.

HivBivus (Sweden)

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

Participating physicians (city): B. Åkerlund (Huddinge); K. Koppel, A. Karlsson (Stockholm); L. Flamholc, C. Håkangård (Malmö).

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Nice HIV Cohort (France)

Central coordination: C. Pradier*, E. Fontas, and C. Caissotti.

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

Clinical research assistant: K. Dollet.

SHCS (Swiss HIV Cohort Study, Switzerland): V. Aubert, J. Barth, M. Battegay, E. Bernasconi, J. Böni, H. C. Bucher, C. Burton-Jeangros, A Calmy, M. Cavassini, M. Egger, L. Elzi, J. Fehr, J. Fellay, H. Furrer (Chairman of the Clinical and Laboratory Committee), C. A. Fux, M. Gorgievski, H. Günthard (President of the SHCS), D. Haerry (deputy of "Positive Council"), B. Hasse, H. H. Hirsch, I. Hösli, C. Kahlert, L. Kaiser, O. Keiser, T. Klimkait, H. Kovari, B. Ledergerber, G. Martinetti, B. Martinez de Tejada, K. Metzner, N. Müller, D. Nadal, G. Pantaleo, A. Rauch (Chairman of the Scientific Board), A. Regenass, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother & Child Substudy), P. Schmid, D. Schultze, F. Schöni-Affolter, J. Schüpbach, R. Speck, P. Taffé, P. Tarr, A. Telenti, A. Trkola, P. Vernazza, R. Weber*, and S. Yerly.