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Opportunistic infections and AIDS malignancies early after initiating combination antiretroviral therapy in high-income countries

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Ethics statement

All cohorts in the HIV-CAUSAL collaboration received approval from their individual ethics review boards. Approval was also given by all ethics review boards to pool anonymised data for analyses and dissemination. Signed informed consent was obtained from all patients.

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Keywords

HIV; Immune reconstitution inflammatory syndrome; unmasking; incidence; inverse probability weighting

Introduction

Combined antiretroviral therapy (cART) has dramatically reduced morbidity and mortality associated with HIV infection[1–4]. cART restores the immune response against opportunistic infections (OIs), but some patients experience an inflammatory reaction within weeks or months after cART initiation[5, 6]. This immune reconstitution inflammatory syndrome (IRIS), whose pathogenesis is not fully elucidated, can result in clinical worsening of existing opportunistic infections after commencing cART (paradoxical IRIS) or in the appearance soon after cART initiation of a new and previously unrecognised opportunistic infections (unmasking IRIS)[7]. IRIS may be associated with significant morbidity, is a diagnostic challenge and complicates clinical management[7].

IRIS has been described in patients with opportunistic infections and AIDS malignancies caused by infections [8–17] as well as in patients with non-infectious conditions such as rheumatoid arthritis and sarcoidosis, although with a different immunopathogenesis [18, 19]. Whereas there is a solid body of literature documenting reactions associated with immune restoration for mycobacterial infections both in the HIV-negative[20] and the HIV-positive population[21–24], our knowledge of IRIS for other conditions is mainly based upon case reports of patients on cART. Most of these describe cases of paradoxical phenomena and only few studies have reported on unmasking IRIS. Further, because case definitions have not been implemented in large observational databases, it has been problematic to estimate its magnitude.

The HIV-CAUSAL Collaboration has recently reported an increase in tuberculosis incidence shortly after cART initiation which was particularly marked in patients with CD4 counts below 50 cells/μL, a pattern strongly suggestive of unmasking IRIS[25]. This pattern was not seen for *Pneumocystis jirovecii* pneumonia. Here we update and extend our study to the effect of cART on AIDS-defining events suggested to be associated with IRIS in the literature: tuberculosis, *mycobacterium avium* complex (MAC), cytomegalovirus (CMV) retinitis, progressive multifocal leukoencephalopathy (PML), herpes simplex virus, Kaposi Sarcoma, Non Hodgkin Lymphoma, cryptococcosis and candidiasis. For each of these AIDS-defining events we explore whether changes in incidence after cART initiation are compatible with unmasking IRIS.

Methods

Study population

We used data from the HIV-CAUSAL collaboration, which includes HIV-positive individuals from prospective cohorts in 6 European countries and the United States[25]. All cohorts are based on routinely collected data in clinical practice within settings with universal access to care. Initiation of cART was defined as the date on which an individual initiated treatment with at least two nucleoside reverse transcriptase inhibitors plus either one or more protease inhibitors, one nonnucleoside reverse transcriptase inhibitors, one entry/fusion inhibitor, or one integrase inhibitor.

Analyses included individuals who were HIV-positive between 1996–2013 aged≥18 years, and had a CD4 count and an HIV-RNA measurement within 6 months of each other while ART naïve. Individuals' follow-up started at baseline, defined as the date when all the inclusion criteria were met, and ended at outcome diagnosis, death, 12 months after the most recent laboratory measurement, or cohort-specific administrative censoring, whichever occurred earlier. To prevent the misclassification of undiagnosed prevalent opportunistic infections and AIDS malignancies as incident cases and thus minimise the inclusion of cases of paradoxical IRIS our analyses excluded HIV-positive individuals who were not AIDS-free during the baseline month.

Outcomes

We considered as primary outcomes all AIDS-events previously suggested to be associated with IRIS. We included tuberculosis, CMV retinitis, cryptococcosis, PML and Kaposi Sarcoma because these were the most common AIDS-defining events in a systematic review of IRIS in observational studies[11]. We included MAC because its association with IRIS was observed soon after antiretroviral therapy was introduced[21]. We included Non-Hodgkin Lymphoma because rare manifestations of IRIS have been reported[10, 26]. We included candidiasis and herpes simplex virus (often not considered in association with IRIS) because a large cohort study of cART initiators in the United States[12] reported them as the most common IRIS-related events.

The diagnostic criteria for the AIDS-defining events[27] were those routinely used in clinical practice in each of the participating countries. Information on use of prophylaxis drugs for these conditions is not collected by the HIV-CAUSAL Collaboration because prophylaxis for these conditions is not widely implemented in most of the participating cohorts.

For each outcome, our working definition for unmasking IRIS was a newly diagnosed and non-previously detected AIDS-defining event in the first three months after starting cART.

Statistical methods

All analyses were conducted separately for each outcome. We computed incidence rates as number of cases per 1000 person-years and estimated the hazard ratio of each outcome for i)

cART versus no cART and ii) no cART versus <3 and ≥3 months since cART initiation. We then estimated the cumulative incidence up to 3 months after cART initiation[28].

To estimate the hazard ratios we used a pooled logistic model for risk of the outcome at month *m*+1 that included a time-varying indicator for ever use of cART through month *m*, month of follow-up *m* (restricted cubic splines with 5 knots) and the following baseline covariates: CD4 cell count (<50,50–99,100–199,200–349,350–499, or ≥500 cells/mm^3), HIV-RNA level (<4,4–5 or >5 log10 copies/mL), sex, transmission group (heterosexual, men who have sex with men, injecting drug users, or other/unknown), calendar year (1996–1998,1999–2000,2001–2003, or 2004–2013), age (<35,35–50, or >50 years), geographical origin (Western countries, sub-Saharan Africa, other, or unknown), time since HIV infection diagnosis (<3 versus ≥3 months) and cohort.

Because cART is more likely to be initiated in individuals with a low CD4 count and a high HIV-RNA level, estimates from the previous models have to be adjusted for these time-dependent confounders. Because CD4 count and HIV-RNA are affected by prior treatment, adding them as time-dependent covariates in the logistic regression model may introduce bias[29]. Therefore we used inverse probability weighting to adjust for time-varying CD4 count and HIV-RNA. Formally, under the assumption that all time-varying predictors of both cART and AIDS were included in the analyses, the weighted model estimates the parameters of a marginal structural Cox model[30].

Each patient in the analysis received a time-dependent weight inversely proportional to the probability of having its own observed history of cART initiation, as described elsewhere[30]. To estimate each patient's probability of cART initiation in each month, we fit a pooled logistic model that included the covariates listed above for the outcome model plus the most recent measurement of the following time-dependent covariates: CD4 cell count (restricted cubic splines with 5 knot), HIV-RNA level (<4, 4–5 or >5 log10 copies/mL), AIDS (yes or no) and time since last laboratory measurement. Inverse probability weights were also estimated to adjust for potential selection bias due to censoring by infrequent measurement. Both the cART initiation and censoring weights were stabilized and their product used to fit the weighted pooled logistic model. To avoid the influence of outliers on the variance of the estimates, we truncated the weights at a maximum of 10 which affected <1% of the individuals. The estimated weights used in the analyses had a mean of 1.01. Truncation did not materially change the hazard ratio estimates. We computed conservative 95% confidence intervals for the log hazard ratio by using a variance estimator that accounts for the estimation of the weights.

We performed several sensitivity analyses: i) we estimated the hazard ratio of no cART versus time since cART initiation categories <4 and ≥4 months, ii) in addition to censoring follow-up at 12 months without a laboratory measurement, we censored at 18 and 24 months after the last measurement, iii) the start of follow-up was delayed by 3 months to exclude prevalent cases, iv) we lagged CD4 count and HIV-RNA level 14 days or 21 days to ensure that cART initiation was predicted using prior measurements, v) we estimated inverse probability weights for censoring by death (so that estimates can be interpreted as if all

deaths could be prevented), and vi) we included patients who started cART during the first month after baseline.

All analyses were conducted with SAS, version 9.3.

Results

Our analysis included 96,562 eligible individuals who contributed 377,324 person-years during a median [interquantile range (IQR)] follow-up of 31 [13, 65] months. Table 1 shows their baseline characteristics: 78% were men and 70% started follow-up after 2000. The median [IQR] CD4 cell count, HIV-RNA and age at baseline were 405 [263,570] cells/mm^3, 4.4 [3.8,5.0] log10 copies/mL and 36 [30,43] years, respectively. Fifty-seven % of the included patients initiated cART during follow-up; the median [IQR] CD4 cell count, HIV-RNA and age at cART initiation were 279 [187,380] cells/mm^3, 4.7 [4.0,5.2] log_{10} copies/mL and 38 (32,46) years, respectively.

The incidence rate (per 1000 person-years) ranged between 2.3 for tuberculosis and 0.3 for CMV retinitis and PML. For all outcomes, incidence rates were lower for higher CD4 cell count, younger age and lower HIV-RNA level at baseline (Figure 1). Appendix 1 shows the number of cases and incidence rates for each outcome by baseline characteristics. The hazard ratios (95% confidence intervals) for cART versus no cART were less than 1 for all outcomes, and ranged between 0.13 (0.05–0.38) for cryptococcosis and 0.76 (0.58–1.00) for herpes simplex infection. Appendix 2 shows the weighted and unweighted hazard ratio estimates.

The median [IQR] CD4 cell count at event diagnosis was 291 [161,440] cells/mm^3 for tuberculosis, 34 [10,189] cells/mm^3 for MAC, 38 [10,189] cells/mm^3 for CMV retinitis, 185 [72,310] cells/mm^3 for PML, 360 [199,535] cells/mm^3 for herpes simplex virus, 322 [186,457] cells/mm^3 for Kaposi Sarcoma, 318 [192,466] cells/mm^3 for Non Hodgkin Lymphoma, 55 [19,149] cells/mm^3 for cryptococcosis and 241 [100,399] cells/mm^3 for candidiasis.

Table 2 presents the hazard ratios of each outcome by time since initiation of cART. Compared with non-cART initiation, the hazard ratios up to 3 months after cART initiation were 1.21 (0.90–1.63) for tuberculosis, 2.61 (1.05–6.49) for MAC, 1.17 (0.34–4.08) for CMV retinitis, 1.18 (0.62–2.26) for PML, 1.21 (0.83–1.75) for herpes simplex virus, 1.18 (0.87–1.58) for Kaposi Sarcoma, 1.56 (0.82–2.95) for Non Hodgkin Lymphoma, 1.11 (0.56–2.18) for cryptococcosis and 0.77 (0.40–1.49) for candidiasis. The hazard ratios ≥3 months since cART initiation compared to non-cART initiation ranged between 0.06 (0.02–0.19) for cryptococcosis and 0.69 (0.51–0.92) for herpes simplex virus. The hazard ratio up to 3 months after cART initiation for any of the explored AIDS event compared to non-cART initiation was 1.25 (1.05,1.48).

The hazard ratio estimates by time since cART initiation stratified by CD4 cell count, HIV-RNA level, age and sex for events with more than 500 cases (tuberculosis, Kaposi Sarcoma, Non Hodgkin Lymphoma, candidiasis and herpes simplex virus) are presented in Appendices 3–7. The risk of tuberculosis up to 3 months after cART initiation was 1.77

(0.78,4.00) in patients with baseline CD4 count <50 cells/mm^3, 2.10 (1.07,4.11) in patients with age>50 years and 1.21 (0.84,1.74) in males.

The hazard ratio estimates did not materially change in sensitivity analyses (Appendix 7). The cumulative incidence (95% confidence intervals) at 3 months following cART initiation ranged between 0.17% (0.14%- 0.20%) for tuberculosis and 0.02% (0.01%- 0.04%) for CMV retinitis. The cumulative incidence for any of the outcomes at 2 months following cART initiation was 0.67% (0.60–0.74%).

Discussion

Our study suggests that cART initiation reduces the overall incidence of tuberculosis, MAC, CMV retinitis, PML, Herpes Simplex virus, Kaposi Sarcoma, Non Hodgkin Lymphoma, cryptococcosis and candidiasis. In spite of this net overall reduction, there was evidence of an increased risk of MAC up to 3 months after cART initiation. The 3-month risk was also slightly elevated for tuberculosis, CMV retinitis, Herpes Simplex virus, Kaposi Sarcoma and Non Hodgkin Lymphoma, but the 95% confidence intervals were wide. The epidemiological patterns observed for MAC and TB are consistent with a relevant proportion of unmasking IRIS among the diagnosis; for the other conditions the evidence is less compelling. For candidiasis the evidence did not support unmasking IRIS.

Our results build on previous findings reported by the HIV-CAUSAL Collaboration with follow-up through 2007. We now report a lower incidence of TB (2.3 versus 3.2 cases per 1000 person-years) and a lower increase in TB incidence soon after cART initiation (21% versus 36%). Since median CD4 cell count at TB diagnosis has not increased over time (results not shown), these changes might be explained by a combination of random variability, temporal trends in TB incidence, and with enhanced pre-cART screening due to increased awareness of TB-related IRIS.

Although IRIS has been most often reported for opportunistic infections, IRIS associated with malignancies has also been described[9, 10]. Like previous studies[31, 32], we found small increases in risk of Non Hodgkin Lymphoma and Kaposi Sarcoma up to 3 months of cART initiation, but the 95% confidence intervals were wide. Given that the development of these cancers should be preceded by exposure to causative agents, the increased incidence for malignancies up to 3 months after cART initiation is consistent with unmasking IRIS leading to increased clinical symptoms and thus diagnostic steps in the case of prevalent subclinical cancers.

We also found that the risk at 3 months of cART initiation for any of the events was <0.7%. This risk is much lower than that reported in a meta-analysis (between 38% for CMV retinitis and 6% for Kaposi Sarcoma)[11] and in the HOPS cohort (between 23% for candidiasis and 0.5% for PML)[12]. Because these previous studies were not restricted to AIDS-free patients, their risk estimates encompass both paradoxical IRIS and unmasking IRIS. In fact, the risk of unmasking IRIS may be even lower because our study cannot distinguish cases of unmasking IRIS from new cases unrelated to IRIS. Further ascertainment bias may account for some of the cases recorded early after cART initiation,

as these might have been previously undiagnosed cases due to more intensive clinical screening in newly treated patients. However, the fact that we found no significant initial increase in risk despite this potential bias strengthens our conclusions that unmasking IRIS for the explored events is not common after cART initiation in patients starting cART in recent times in the European and North American setting.

Our study had several limitations. First, like all observational studies the validity of our estimates relies on the assumption of no unmeasured confounding. Although we adjusted our models for CD4 count and HIV-RNA levels, the most important factors used by clinicians to decide whether to start cART, we cannot exclude the possibility that other unmeasured variables related to cART initiation could have also played a role. Second, we assumed that patients remained on therapy once it was initiated. If the diagnoses of the examined AIDS-defining events were largely occurring in individuals who had stopped cART or had poor adherence, then we might have underestimated the effect of cART initiation on the risk of the explored events. On the other hand, this bias is unlikely to have affected our conclusions on the trends in incidence up to 3 months after cART initiation. Finally, given the small number of events occurring during the first months of cART for some of the outcome events, we could not yet explore whether the effect of cART differed by patients characteristics that may be associated with development of IRIS. This is particularly important for baseline CD4 count[11, 25] because unmasking IRIS is mainly observed in patients with very low CD4 counts, who were a minority in our study population.

In summary, this study suggests that, with the exception of mycobacterial infections, unmasking IRIS is not common after cART initiation in AIDS-free patients in Europe and the United States. In order to make an early diagnosis and provide adequate treatment, clinicians should rule out MAC and TB meticulously in patients at risk before starting cART and monitor closely for these OIs during the early phases of treatment.

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Appendix

Appendix 1. Incidence rates (per 1000 person-years) of AIDS-defining events overall and by baseline characteristics, HIV-CAUSAL Collaboration 1996–2013

	Tuberculosis		MAC		CMV retinitis		PML		Herpes Simplex Virus		Kaposi Sarcoma		Non Hodgkin Lymphoma		Candidiasis		Cryptococcosis	
Variable level	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**
Overall	898	2.3	163	0.4	105	0.3	113	0.3	620	1.6	748	1.9	488	1.2	535	1.4	139	0.35
CD4 count, cells/mm^3																		
<50	87	6	84	5.8	47	3.2	24	1.6	66	4.6	64	4.4	28	1.9	60	4.1	57	3.9
50 – 100	64	4.8	19	1.4	13	1	15	1.1	41	3.1	38	2.9	31	2.3	43	3.2	22	1.6
100 – 200	138	3.7	22	0.6	13	0.3	21	0.6	67	1.8	65	1.7	69	1.8	70	1.9	20	0.5
200 – 350	239	2.6	17	0.2	17	0.2	19	0.2	124	1.4	170	1.9	117	1.3	109	1.2	18	0.2
350 – 500	171	1.7	12	0.1	9	0.1	16	0.2	140	1.4	177	1.8	114	1.1	110	1.1	9	0.1
>500	199	1.5	9	0.1	6	0	18	0.1	182	1.4	234	1.8	129	1	143	1.1	13	0.1
HIV-RNA, copies/mL																		
<10,000	185	1.6	8	0.1	10	0.1	16	0.1	171	1.5	111	0.9	93	0.8	82	0.7	17	0.1
10,000 – 100,000	414	2.3	53	0.3	33	0.2	38	0.2	266	1.5	350	2	224	1.3	234	1.3	50	0.3
≥100000	299	3.1	102	1.1	62	0.6	59	0.6	183	1.9	287	3	171	1.8	219	2.3	72	0.7
Sex																		
Male	618	2	144	0.5	89	0.3	94	0.3	531	1.7	707	2.3	428	1.4	394	1.3	121	0.4
Female	280	3.4	19	0.2	16	0.2	19	0.2	89	1.1	41	0.5	60	0.7	141	1.7	18	0.2
Age, years																		
< 35	383	2.2	39	0.2	26	0.1	26	0.1	191	1.1	262	1.5	140	0.8	220	1.3	31	0.2
35 – 50	389	2.3	99	0.6	55	0.3	61	0.4	322	1.9	364	2.2	242	1.4	241	1.4	83	0.5
>50	126	2.7	25	0.5	24	0.5	26	0.5	107	2.3	122	2.6	106	2.2	74	1.6	25	0.5
Transmission group																		
Heterosexual	426	3.6	30	0.2	15	0.1	21	0.2	69	0.6	98	0.8	122	1	188	1.6	23	0.2
Homo/bi-sexual	147	0.9	34	0.2	18	0.1	40	0.2	104	0.6	482	2.8	235	1.4	178	1	19	0.1
Injection drug-use	86	2.8	14	0.5	5	0.2	13	0.4	18	0.6	9	0.3	43	1.4	124	4.1	9	0.3
Other/unknown	239	3.5	85	1.2	67	1	39	0.6	429	6.5	159	2.3	88	1.3	45	0.7	88	1.3
Geographical origin																		
Western Countries	251	1.4	50	0.3	25	0.1	51	0.3	88	0.5	337	1.8	253	1.4	292	1.6	25	0.1
Sub-Saharan Africa	298	6.6	6	0.1	4	0.1	9	0.2	32	0.7	57	1.2	49	1.1	53	1.1	10	0.2
Rest of World	82	3.2	4	0.2	2	0.1	6	0.2	22	0.8	35	1.4	24	0.9	50	1.9	7	0.3

	Tuberculosis		MAC		CMV retinitis		PML		Herpes Simplex Virus		Kaposi Sarcoma		Non Hodgkin Lymphoma		Candidiasis		Cryptococcosis	
Variable level	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**
Unknown country	267	2	103	0.8	74	0.5	47	0.3	478	3.6	319	2.4	162	1.2	140	1	97	0.7
Calendar period																		
1996 – 1998	240	2	55	0.5	48	0.4	33	0.3	230	2	211	1.8	143	1.2	223	1.9	42	0.4
1999 – 2000	117	2.5	26	0.6	15	0.3	16	0.3	89	1.9	87	1.9	62	1.3	74	1.6	31	0.7
2001–2003	239	3	35	0.4	23	0.3	23	0.3	150	1.9	164	2	108	1.3	109	1.3	32	0.4
2004 – 2013	302	2.1	47	0.3	19	0.1	41	0.3	151	1	286	2	175	1.2	129	0.9	34	0.2

CMV cytomegalovirus; MAC Mycobacterium avium complex; PML Progressive multifocal leukoencephalopathy;

Appendix 2. Hazard ratios of AIDS-defining events for cART initiation versus no cART from unweighted and inverse probability weighted models, HIV-CAUSAL Collaboration 1996–2013

	Unweighted models – baseline covariates	Unweighted models – baseline covariates and time-varying covariates	Weighted models – baseline covariates
Tuberculosis	0.77 (0.65,0.91)	0.95 (0.80,1.12)	0.48 (0.36,0.64)
MAC	1.12 (0.75,1.69)	1.25 (0.84,1.86)	0.51 (0.27,0.95)
CMV Retinitis	0.86 (0.52,1.42)	0.95 (0.58,1.54)	0.24 (0.09,0.66)
PML	1.04 (0.63,1.72)	1.03 (0.63,1.67)	0.41 (0.15,1.09)
Herpes Simplex Infection	0.97 (0.78,1.19)	1.09 (0.88,1.34)	0.76 (0.58,1.00)
Kaposi Sarcoma	0.53 (0.44,0.64)	0.84 (0.70,1.02)	0.22 (0.15,0.32)
Non Hodgkin Lymphoma	0.88 (0.69,1.11)	0.94 (0.74,1.20)	0.51 (0.36,0.73)
Cryptococcosis	0.46 (0.30,0.70)	0.57 (0.38,0.87)	0.15 (0.05,0.42)
Candidiasis	0.43 (0.34,0.54)	0.73 (0.58,0.90)	0.18 (0.12,0.26)

cART Combined antiretroviral therapy; CMV cytomegalovirus; MAC Mycobacterium avium complex; PML Progressive multifocal leukoencephalopathy.

Appendix 3. Hazard ratios of tuberculosis by time since initiation of combined antiretroviral therapy and baseline characteristics, HIV-CAUSAL Collaboration 1996–2013

	No cART initiation		Time since cART initiation, <3 months		Time since cART initiation, ≥3 months	
Baseline characteristics	**Cases, N**	**HR**	**Cases, N**	**HR**	**Cases, N**	**HR**
CD4 count, cells/mm^3						
<50	16	1	24	1.77 (0.78–4.00)	47	0.61 (0.24–1.56)
50 – 100	21	1	14	0.94 (0.42–2.12)	29	0.38 (0.21–0.63)
100 – 200	44	1	17	0.77 (0.41–1.43)	77	0.37 (0.21–0.63)
200 – 350	107	1	26	0.92 (0.51–1.67)	106	0.28 (0.15–0.53)
≥350	234	1	16	1.06 (0.49–2.28)	120	0.43 (0.29–0.63)
HIV-RNA, log10 copies/mL						
<4	113	1	14	1.56 (0.73–3.33)	58	0.45 (0.25–0.81)
4–5	203	1	34	1.25 (0.78–2.01)	177	0.40 (0.27–0.58)
>5	106	1	49	0.96 (0.63–1.47)	144	0.29 (0.16–0.55)
Age, years						
< 35	188	1	38	1.2 (0.73–1.98)	157	0.36 (0.24–0.55)
35 – 50	180	1	37	0.9 (0.58–1.40)	172	0.35 (0.21–0.57)
≥50	54	1	22	2.1 (1.07–4.11)	50	0.38 (0.16–0.90)
Sex						
Male	288	1	70	1.21 (0.84–1.74)	259	0.31 (0.21–0.47)

Baseline characteristics	No cART initiation		Time since cART initiation, <3 months		Time since cART initiation, ≥3 months	
	Cases, N	HR	Cases, N	HR	Cases, N	HR
Female	133	1	27	1.12 (0.67–1.88)	120	0.44 (0.29–0.67)

Appendix 4. Hazard ratios of Kaposi Sarcoma by time since initiation of combined antiretroviral therapy and baseline characteristics, HIV-CAUSAL Collaboration 1996–2013

Baseline characteristics	No cART initiation		Time since cART initiation, <3 months		Time since cART initiation, ≥3 months	
	Cases, N	HR	Cases, N	HR	Cases, N	HR
CD4 count, cells/mm^3						
<50	21	1	15	0.92 (0.46–1.82)	28	0.24 (0.09–0.65)
50 – 100	13	1	8	0.67 (0.24–1.87)	17	0.12 (0.04–0.39)
100 – 200	30	1	12	0.62 (0.31–1.22)	23	0.05 (0.01–0.19)
200 – 350	81	1	16	0.73 (0.41–1.32)	73	0.16 (0.09–0.29)
≥350	259	1	44	1.76 (1.13–2.74)	108	0.19 (0.12–0.29)
HIV-RNA, log10 copies/mL						
<4	59	1	13	1.56 (0.73–3.33)	39	0.31 (0.15–0.64)
4–5	192	1	43	1.25 (0.78–2.01)	115	0.13 (0.07–0.24)
>5	153	1	39	0.96 (0.63–1.47)	95	0.15 (0.09–0.24)
Age, years						
< 35	151	1	34	1.2 (0.73–1.98)	77	0.06 (0.03–0.1.2)
35 – 50	198	1	49	0.9 (0.58–1.40)	117	0.19 (0.11–0.33)
≥50	55	1	12	2.1 (1.07–4.11)	55	0.32 (0.15–0.69)
Sex						
Male	392	1	89	1.21 (0.84–1.74)	226	0.14 (0.10–0.21)
Female	12	1	6	1.12 (0.67–1.88)	23	0.12 (0.02–0.71)

Appendix 5. Hazard ratios of Non Hodgkin Lymphoma by time since initiation of combined antiretroviral therapy and baseline characteristics, HIV-CAUSAL Collaboration 1996–2013

Baseline characteristics	No cART initiation		Time since cART initiation, <3 months		Time since cART initiation, ≥3 months	
	Cases, N	HR	Cases, N	HR	Cases, N	HR
CD4 count, cells/mm^3						
<50	9	1	3	0.59 (0.25–1.40)	16	0.18 (0.09–0.35)

	No cART initiation		Time since cART initiation, <3 months		Time since cART initiation, ≥3 months	
Baseline characteristics	**Cases, N**	**HR**	**Cases, N**	**HR**	**Cases, N**	**HR**
50 – 100	9	1	2	0.33 (0.06–1.71)	20	0.08 (0.02–0.29)
100 – 200	15	1	6	0.16 (0.05–0.55)	48	0.15 (0.05–0.44)
200 – 350	40	1	12	1.33 (0.34–5.13)	65	0.11 (0.05–0.25)
≥350	125	1	15	1.52 (0.79–2.93)	103	0.37 (0.23–0.59)
HIV-RNA, log10 copies/mL						
<4	54	1	4	0.63 (0.16–22.43)	35	0.49 (0.24–0.99)
4–5	98	1	18	1.20 (0.4–3.52)	108	0.11 (0.06–0.19)
>5	46	1	16	0.44 (0.26–0.74)	109	0.14 (0.09–0.22)
Age, years						
< 35	68	1	9	0.26 (0.12–0.58)	63	0.12 (0.06–0.23)
35 – 50	100	1	26	1.24 (0.52–2.95)	116	0.12 (0.07–0.20)
≥50	30	1	3	0.44 (0.15–1.32)	73	0.22 (0.09–0.56)
Sex						
Male	163	1	35	0.89 (0.40–1.98)	229	0.13 (0.08–0.21)
Female	35	1	2	0.46 (0.18–1.17)	3	0.13 (0.06–0.26)

Appendix 6. Hazard ratios of Candidiasis by time since initiation of combined antiretroviral therapy and baseline characteristics, HIV-CAUSAL Collaboration 1996–2013

	No cART initiation		Time since cART initiation, <3 months		Time since cART initiation, ≥3 months	
Baseline characteristics	**Cases, N**	**HR**	**Cases, N**	**HR**	**Cases, N**	**HR**
CD4 count, cells/mm^3						
<50	20	1	11	0.59 (0.25–1.40)	29	0.18 (0.09–0.35)
50 – 100	20	1	3	0.33 (0.06–1.71)	20	0.08 (0.02–0.29)
100 – 200	26	1	3	0.16 (0.05–0.55)	41	0.15 (0.05–0.04)
200 – 350	53	1	9	1.33 (0.34–5.13)	47	0.11 (0.05–0.25)
≥350	156	1	10	0.62 (0.22–1.73)	87	0.17 (0.11–0.29)
HIV-RNA, log10 copies/mL						
<4	47	1	3	0.63 (0.16–2.43)	32	0.49 (0.24–0.99)
4–5	129	1	12	1.20 (0.41–3.52)	93	0.11 (0.06–0.19)
>5	99	1	21	0.44 (0.26–0.74)	99	0.14 (0.09–0.22)
Age, years						
< 35	111	1	8	0.26 (0.12–0.58)	101	0.12 (0.06–0.23)
35 – 50	137	1	24	1.24 (0.52–2.95)	80	0.12 (0.07–0.20)
≥50	27	1	4	0.44 (0.15–1.32)	43	0.22 (0.09–0.56)

Baseline characteristics	No cART initiation		Time since cART initiation, <3 months		Time since cART initiation, ≥3 months	
	Cases, N	HR	Cases, N	HR	Cases, N	HR
Sex						
Male	205	1	27	0.89 (0.40–1.98)	162	0.13 (0.08–0.21)
Female	70	1	9	0.46 (0.18–1.17)	62	0.13 (0.06–0.26)

Appendix 7. Hazard ratios of Herpes Simplex Virus by time since initiation of combined antiretroviral therapy and baseline characteristics, HIV-CAUSAL Collaboration 1996–2013

Baseline characteristics	No cART initiation		Time since cART initiation, <3 months		Time since cART initiation, ≥3 months	
	Cases, N	HR	Cases, N	HR	Cases, N	HR
CD4 count, cells/mm^3						
<100	23	1	13	1.02 (0.49–2.13)	71	0.38 (0.19–0.78)
100 – 200	15	1	4	0.58 (0.19–1.77)	48	1.02 (0.39–2.64)
200 – 350	41	1	6	0.90 (0.35–2.31)	77	0.98 (0.56–1.71)
≥350	175	1	19	1.43 (0.84–2.43)	128	0.67 (0.46–0.98)
HIV-RNA, log10 copies/mL						
<4	92	1	10	1.60 (0.75–3.40)	69	0.74 (0.44–1.24)
4–5	109	1	15	1.11 (0.60–2.04)	142	0.74 (0.49–1.11)
>5	53	1	17	0.97 (0.55–1.73)	113	0.59 (0.29–1.18)
Age, years						
< 35	91	1	13	1.04 (0.53–2.01)	87	0.56 (0.33–0.95)
35 – 50	119	1	22	1.58 (0.96–2.59)	181	0.82 (0.55–1.23)
≥50	44	1	7	0.65 (0.26–1.66)	56	0.56 (0.27–1.16)
Sex						
Male	216	1	36	1.28 (0.85–1.92)	276	0.68 (0.49–0.93)
Female	38	1	6	0.79 (0.31–2.00)	45	0.70 (0.32–1.57)

Appendix 8. Sensitivity analyses. Hazard ratios (95% confidence intervals) for combined antiretroviral therapy initiation versus time since cART initiation <3 months, HIV-CAUSAL Collaboration 1996–2013

	Main analysis (time since cART initiation <3 months)	Time since cART initiation <4 months	Not excluding patients who initiated cART in the first month after baseline	Start of follow up delayed by 3 months	Inverse probability weights for censoring by death	CD4 count and HIV RNA lagged by 14 days	CD4 count and HIV RNA lagged by 21 days	Censoring at 18 months	Censoring at 24 months
Tuberculosis	1.21 (0.90–1.63)	0.99 (0.75–1.30)	1.38 (1.04–1.83)	1.61 (1.00–2.59)	1.21 (0.90–1.64)	1.27 (0.95–1.70)	1.26 (0.93–1.69)	1.28 (0.95–1.71)	1.34 (1.00–1.79)
MAC	2.61 (1.05–6.49)	2.07 (0.91–4.70)	2.25 (1.10–4.62)	2.87 (1.15–7.16)	2.87 (1.15–7.16)	2.03 (1.19–3.47)	2.25 (1.31–3.86)	2.56 (1.07–6.12)	2.98 (1.39–6.42)
CMV Retinitis	1.17 (0.34–4.08)	0.84 (0.26–2.70)	1.18 (0.40–3.44)	1.52 (0.23–10.8)	1.20 (0.35–4.11)	1.26 (0.33–4.77)	1.27 (0.30–5.33)	1.38 (0.42–4.51)	1.46 (0.46–4.66)
PML	1.18 (0.62–2.26)	1.41 (0.78–2.55)	1.56 (0.78–3.13)	1.02 (0.38–2.74)	1.19 (0.63–2.27)	1.17 (0.60–2.28)	1.19 (0.59–2.38)	1.23 (0.67–2.24)	1.46 (0.82–2.59)
Herpes Simplex Infection	1.21 (0.83–1.75)	1.22 (0.88–1.69)	0.81 (0.62–1.05)	0.92 (0.53–1.59)	1.18 (0.81–1.72)	1.19 (0.82–1.73)	1.27 (0.87–1.85)	1.66 (1.00–2.74)	1.72 (1.04–2.84)
Kaposi Sarcoma	1.18 (0.87–1.58)	1.02 (0.71–1.45)	1.12 (0.84–1.48)	1.02 (0.71–1.45)	1.18 (0.88–1.58)	1.34 (1.00–1.78)	1.34 (1.00–1.78)	1.24 (0.93,1.64)	1.31 (0.99–1.73)
Non Hodgkin Lymphoma	1.56 (0.82–2.95)	1.55(0.86–2.77)	1.52 (0.96–2.42)	1.88 (0.82–4.27)	1.54 (0.82–2.92)	1.72 (0.89–3.32)	1.72 (0.89–3.32)	1.56 (0.86–2.85)	0.79 (0.42–1.49)
Cryptococcosis	1.11 (0.56–2.18)	0.77 (0.40–1.48)	1.21 (0.60–2.46)	1.07 (0.35–3.27)	1.48 (0.57–3.80)	1.05 (0.53–2.10)	1.06 (0.53–2.11)	1.28 (0.67–2.46)	0.99 (0.56–1.75)
Candidiasis	0.77 (0.40–1.49)	0.53 (0.28–1.02)	0.78 (0.49–1.25)	0.98 (0.38–2.54)	0.76 (0.39–1.48)	0.83 (0.41–1.66)	0.82 (0.40–1.69)	0.75 (0.39–1.43)	0.75 (0.39–1.43)

CMV cytomegalovirus; MAC Mycobacterium avium complex; PML Progressive multifocal leukoencephalopathy.

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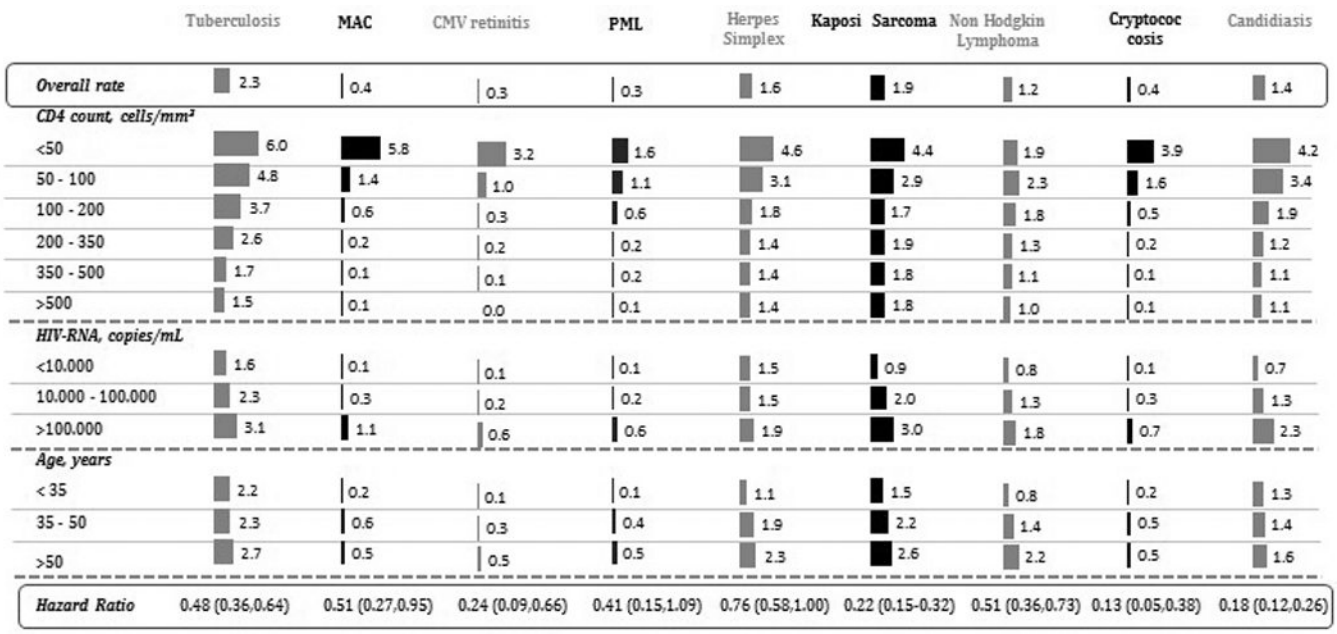

Figure 1.

Incidence rates of AIDS-defining events per 1000 person-year of follow-up, HIV-CAUSAL Collaboration 1996–2013

cART Combined antiretroviral therapy; CMV cytomegalovirus; MAC Mycobacterium avium complex; PML Progressive multifocal leukoencephalopathy.

Table 1

Baseline characteristics of study participants, HIV-CAUSAL Collaboration 1996–2013

	Individuals	Median [IQR] follow-up months	Person years	cART Initiators (%)
CD4 count, cells/mm^3				
<50	3522	27 [11, 64]	13088.33	2784 (79%)
50 – 100	3061	33[12, 71]	12360.83	2468 (81%)
100 – 200	8641	34[14, 73]	35951.17	7018 (81%)
200 – 350	21807	33[14, 70]	88392.08	15648 (72%)
350 – 500	24553	31[14, 67]	96822	13854 (56%)
>500	34978	30[13, 62]	130709.67	13372 (38%)
HIV-RNA, log10 copies/mL				
<4	30596	29[13, 61]	114836.42	12650 (41%)
4–5	43419	32[14, 67]	171358	25928 (60%)
>5	22547	34[14, 71]	91129.67	16566 (73%)
Sex				
Male	75049	32[14, 67]	295646.25	43038 (57%)
Female	21513	29[13, 65]	81677.83	12106 (56%)
Age, years				
< 35	44698	30[13, 63]	169760.17	23362 (52%)
35 – 50	40154	33[14, 70]	162430.83	23980 (60%)
≥50	11710	32[12, 67]	45133.08	7802 (67%)
Transmission group				
Heterosexual	30060	31[14, 67]	117387.58	17814 (59%)
Homo/bi-sexual	39971	35[16, 71]	166591.83	23014 (58%)
Injection drug-use	8201	24[11, 56]	29432.17	3817 (47%)
Other/unknown	18330	26[11, 58]	63912.5	10499 (57%)
Geographical origin				
Western Countries	57041	31[13, 67]	224174.75	32765 (57%)
Sub-Saharan Africa	12497	29[13, 62]	44686.75	7453 (60%)
Rest of World	7577	27[13, 55]	25211.42	4054 (54%)
Unknown country	19447	34[15,74]	83251.17	10872 (56%)
Calendar period				
1996 – 1998	20317	38 [14, 118]	112796.42	11251 (55%)
1999 – 2000	8940	40[14, 110]	44845.33	5276 (59%)
2001 – 2003	16639	43[16, 98]	77702	9742 (59%)
2004–2013	50666	27 [12,50]	141980.33	28875 (57%)
Overall	96562	31 [13,65]	377324.08	55144 (57%)

cART. Combined antiretroviral therapy; IQR. Interquantile range.

Table 2

Hazard ratios of AIDS-defining events by time since initiation of combined antiretroviral therapy, HIV-CAUSAL Collaboration 1996–2013

	Time since cART initiation	N cases	Person-years	Incidence rates of events per 1000 person year	Hazard Ratio (95% confidence intervals)
Tuberculosis	No cART	422	143523.33	2.9	1
	<3 months	97	9259.00	10.5	1.21 (0.90–1.63)
	≥3 months	379	236095.92	1.6	0.36 (0.26–0.49)
Mycobacterium Avium Complex	No cART	46	143936.50	0.3	1
	<3 months	37	9306.83	4.0	2.61 (1.05–6.49)
	≥3 months	80	238799.67	0.3	0.31 (0.16–0.59)
CMV Retinitis	No cART	35	143938.83	0.2	1
	<3 months	12	9308.42	1.3	1.17 (0.34,4.08)
	≥3 months	58	238917.67	0.2	0.13 (0.04–0.39)
PML	No cART	38	143944.00	0.3	1
	<3 months	19	9307.42	2.0	1.18 (0.62–2.26)
	≥3 months	56	238960.75	0.2	0.21 (0.06–0.71)
Herpes Simplex Virus	No cART	254	143476.42	1.8	1
	<3 months	42	9282.00	4.5	1.21 (0.83–1.75)
	≥3 months	324	236713.50	1.4	0.69 (0.51–0.92)
Kaposi Sarcoma	No cART	404	143755.17	2.8	1
	<3 months	95	9250.67	10.3	1.18 (0.87–1.58)
	≥3 months	249	236065.50	1.1	0.14 (0.10–0.21)
Non Hodgkin Lymphoma	No cART	198	143875.92	1.4	1
	<3 months	38	9288.17	4.1	1.56 (0.82–2.95)
	≥3 months	252	237871.50	1.1	0.40 (0.27–0.58)
Cryptococcosis	No cART	60	143924.67	0.4	1
	<3 months	21	9305.67	2.3	1.11 (0.56,2.18)
	≥3 months	58	238860.92	0.2	0.06 (0.02–0.19)
Candidiasis	No cART	275	143745.33	1.9	1
	<3 months	36	9275.67	3.9	0.77 (0.40–1.49)
	≥3 months	224	237213.75	0.9	0.13 (0.09–0.20)

cART Combined antiretroviral therapy; CMV cytomegalovirus; MAC Mycobacterium avium complex; PML Progressive multifocal leukoencephalopathy.